Department of Health and Human Services

Public Health Service

Centers for Disease Control and Prevention

Advisory Committee on Immunization Practices

Minutes of the Meeting

June 19-20, 1996

Atlanta, Georgia

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
CENTERS FOR DISEASE CONTROL AND PREVENTION
ATLANTA, GEORGIA
AUDITORIUM B
JUNE 19-20, 1996

JUNE 19

8:30	Welcome		Dr. J. Davis Dr. D. Snider
9:00	Public Comment: Polio Vaccination Recommendation and Schedule	Information	Dr. D. Satcher Dr. J. Davis
12:00	LUNCH		
1:00	Measles, Mumps, and Rubella (MMR) Policy Statement	Draft Statement	Dr. J. Modlin Dr. E. Thompson NIP Staff
	Vaccination of HIV-Infected Persons with MMR	Discussion	Dr. N. Halsey Dr. J. Modlin Dr. D. Scheifele Dr. W. Schluter Dr. J. Watson
3:00	BREAK		
3:30	Hepatitis A for Special Groups in the Vaccines for Children Program	Vote	Dr. H. Margolis
4:00	Status of Hepatitis B Statement	Information	Dr H. Margolis
4:15	Draft Statement for Rabies Post-Exposure Treatment	Draft Statement	Dr. C. Rupprecht
5:15	Programmatic Issues Regarding Computerized Immunization Records -- Timing DTP4	Discussion	Dr. K. Bisgard
5:45	ADJOURN		

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
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JUNE 20

8:30	Committee Discussion of Draft Poliomyelitis Recommendation and Schedule	Decision	Dr. R. Prevots Dr. J. Ward
10:30	BREAK		
11:00	Draft Statement on Acellular Pertussis Vaccine	Draft Statement	Dr. D. Guris Dr. P. Strebel
12:30	LUNCH		
1:30	Vaccination of Premature Infants	Information	Dr. G. Losonsky
2:00	Update on Vaccine Injury Compensation Program	Information	Dr. G. Evans
2:10	Update on National Vaccine Program	Information	Dr. R. Breiman
2:20	Unfinished Business		Dr. J. Davis
2:50	Public Comment		
3:05	ADJOURN		

ATTENDEES:

Committee Members
Dr. Jeffrey Davis (Chair)
Dr. Barbara Ann DeBuono
Dr. Mary Glode
Dr. Marie Griffin
Dr. Fernando Guerra
Dr. John Modlin
Dr. Jessie Sherrod
Dr. Steve Schoenbaum
Dr. F. E. Thompson
Dr. Joel Ward

Ex Officio Members
Dr. Robert Breiman (NVPO)
Dr. Geoffrey Evans (VICP)
Dr. Carolyn Hardegree (FDA)
Mr. Randolf Graydon (HCFA)
Dr. Kristin Nichol (VA)
Col. Relford Patterson (DOD)
Dr. G. Rabinovich (NIAID)

Liaison Representatives
Dr. Richard Clover (ATPM)
Dr. David Fleming (HICPAC)
Dr. Stanley Gall (ACOG)
Dr. Pierce Gardner (ACP)
Dr. William Glezen (IDSA)
Dr. Neal Halsey (AAP)
Dr. Suzane Jenkins, (NASPHV)
Dr. Georges Peter (AAP)
Dr. William Schaffner (AHA)
Dr. David Scheiffle (NACI)
Mr. David Williams (PhARMA)
Dr. Richard Zimmerman (AAFP)

Executive Secretary
Dr. Dixie Snider

Office of the Director
Dr. David Satcher

Office of the General Counsel
Mr. Kevin Malone
Mr. Gene Mathews

Office of Public Affairs
Barbara Reynolds

Epidemiology Program Office
Nadine Martin
Lanette Wolcott

National Center for Infectious Diseases
Dr. Miriam Alter
Dr. Beth Bell
Dr. Olen Kew
Dr. John Krebs
Dr. Frank Mahoney
Dr. Mark Pallansch
Dr. Sleda Perryman
Dr. Craig Shapiro

National Immunization Program
Dr. William Atkinson
Dr. Sue Bath
Dr. Kris Bisgard
Dr. Bob Chen
Dr. Jenny Coley
Dr. Jose Cordero
Dr. Victor Coronado
Dr. Shalini Desai
Dr. Vance Dietz
Dr. Clare Dykewicz
Dr. Jessica Emelin
Dr. Gary Euler
Ms. Judy Gantt
Dr. Paul Garrison
Ms. Edith Gary
Dr. Jacqueline Gindler
Dr. Dalya Guris
Dr. Steve Hadler
Dr. Edward Hoekstra
Dr. Murial Hoyt
Dr. Sonja Hutchins
Ms. Lauri Johnson
Ms. Jacqueline Kellachan
Mr. Paul Kilgore
Ms. Maureen Kolaso
Dr. Charles LeBaron

Attendees Continued:

National Immunization Program

Dr. John Livengood
Dr. Romney Norwood
Dr. Walt Orenstein
Dr. Rebecca Prevots
Dr. Susan Reef
Mr. Anthony Scardaci
Dr. Will Schluter
Dr. Rina Shaikh
Dr. Abby Shefer
Dr. Ray Strikas
Mr. Robert Snyder
Dr. Peter Strebel
Dr. Gina Terraceiano
Dr. Ann Thomas
Dr. Frederick Van Loon
Dr. Jay Watson
Dr. Melinda Wharton
Dr. Ian Williams
Dr. Walter Williams
Dr. Fuyuen Yip

Other Government Attendees

Dr. Bruce Gellen, NIH
Dr. Peter Patriarca, FDA

Others Present

Bob Adams, Journalist
Cynthia Arnold, DACK
Janice Barrocas, APPA
Ana Rivas-Beck, COSSMHO
Dee Breeden, S.C. Department of Health
Ralph Buncher, Institute for Science and Public Policy
Victor Caceres, SCDHEC
George Carlo, Institute for Science and Public Policy
Jill Chamberlain, Vaccine Bulletin
Paul Coplan, Merck & Co. Inc.
David Corllery, Ogilvy
Dack Dalrymple, Bailey and Robinson
Corry Dekker, Chiron Biocene
Gary Dubin, M.D., SmithKline Beecham Pharmaceuticals
Philippe Ducios, LCDC, Canada
Ruth Ann Dunn, M.D., Michigan Department of Health
Kenneth Evans, M.D., AAFP
Gretchen K. Findlay, Institute for Science and Public Policy
Rebecca Fish, Merck Vaccine Division
Kristina Fjeld, ASTHO
Graham Gardner, Merck Vaccine Division
Daniel Gennevois, Chiron Biocine
Linda Golodner, National Consumers League
Jesus Gonzalez-Lama, Madrid, Spain
Elizabeth Goss, Fox, Bennett & Turner
Chris Grant, Connaught Laboratories
Jesse Greene, S.C. Department of Health

Attendees Continued:

George Guao
Jill Hackell, Wyeth-Lederle Vaccines
Celine Hanson, BQOM
Betsy Harris, NBNA
Bill Hausdorff, Lederle-Praxis
Evy Hay, MAP International
Susan Hayes, Cooney Waters
Nielson Hobbs, The Blue Sheet
Mark Holdeman, Connaught Labortories, Inc.
John Hollister, SmithKline Beecham
Stephen Hooker, U.S. Navy
Mike Hounshell, Chiron
Lauri Hunter, APPA
B. Icnudsen, Statens Serum Institute, Denmark
Rudolph Jackson, M.D., Morehouse School of Medicine
Samuel L. Katz, M.D., Duke University Medical Center
Dr. Alan Kendal, Emory School of Public Health
Mary Kopp, American Nurses Foundation
Michael Langan, National Organization for Rare Disorders
Jean Lans, Pasteur Merieux Connaught
Marta de Lauo, Montepellier, France
Len Lavenda, Connaught Laboratories
Lucinda Long, Wyeth Ayerst
Genevieve Losonsky, University of Maryland
Dr. Yvonne McHugh, Chiron Biocine
Charles Marwick, Journal of the American Medical Association
Carlton Meschievitz, Connaught
Charles Moorman, Grandparent of child with VAPP
Thomas Moran, Immune Deficiency Foundation
Alan Mothner, Assoicated Press
David Nalin, M.D., Merck Research Laboratories
Bruno Ovry, Montepellier, France
Mahin Para, Georgia Public Health Laboratories
Peter Paradiso, Wyeth Lederle Vaccines
Gordon Pierson, child with VAPP
Randy Pierson, parent of child with VAPP
Susan Pierson, parent of child with VAPP
Stanley Plotkin, M.D., Pasteur Merieux
Susana Revello, Univeristy of LaPaz, Bolivia
Jeff Richards
J.B. Rosefsky, M.D., Wyeth Ayerst Laboratories
John Salamone, ACCV and parent of vaccine polio victim
Bob Sherman, Connaught Laboratories
Judith Shindman, Connaught Laboratories Ltd.

Attendees Continued:

Donna Shomen, SKB
Howard R. Six, Connaught Laboratories Inc.
Garnett H. Slatton, St. Simons Island, Georgia
Natalie Smith, California Department of Health Services
Dan Soland, SmithKline Beecham
Lynne Sommer, NVIC
Ling Su, Merck Research Labs
Karen Sutherland, MCS
Frederique Tarrieu, Montepellier, France
Miriam Tucker, Pediatric News
Sam Turner, Fox, Bennett, Turner
Thomas M. Vernon, Merck Vaccine Division
Emmanuel Vidor, Pasteur Merieux Connaught
Ted Vigodsky, Georgia News Network
M.J. Volpe, Institute for Science
Meg Walsh, KPR
Wanda Warren, SmithKline Beecham
Beth Waters, Cooney Waters
David Weeda, Olsson, Frank & Weeda
Harvey Wilcox, father of child with VAPP
Jerry Winkelstein, M.D., Immune Deficiency Foundation
J.W. Womack, CBS News

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CENTERS FOR DISEASE CONTROL AND PREVENTION

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES
Minutes of the Meeting
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Opening Comments
The Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention (CDC) on June 19-20, 1996. Chairman Dr. Jeffrey Davis began the meeting at 8:40 A.M. Dr. Dixie Snider, CDC's Associate Director of Science, also welcomed the attenders, and introduced CDC Director Dr. David Satcher.

Dr. Satcher applauded ACIP's important contributions to addressing difficult national issues of public health. This meeting's discussion on revising the polio vaccination schedule would be no exception. He also appreciated the experience, perspectives and concern brought by those present who were not on the Committee. He stressed the importance of attending to all points of view on these complex issues, as America's public health pertains to that of the global community.

Dr. Davis made several announcements. The minutes of the February 1996 ACIP meeting would be distributed upon completion and acceptance. A list of 1997 ACIP meeting dates was distributed (February 12/13, June 18/19, October 22/23), as were the BCG/Influenza recommendations recently published in *MMWR*. Dr. Davis solicited the members' completed financial disclosure forms, and detailed the regulations governing conflict of interest disclosure.

Reporting no conflict of interest were Drs. DeBuono and Davis. Dr. Modlin and his wife own a small amount of stock in Merck Corporation and Chiron Corporation, and he had received stipends in the past from Pasteur-Mérieux Connaught for research and educational activities. Dr. Griffin spoke at a scientific symposium sponsored by Atra Pharmaceuticals. Dr. Guerra is currently the principal investigator for North American Vaccine's acellular pertussis field trial in San Antonio, and recently had received a small grant from Merck Vaccine for a hepatitis A community demonstration project.

Dr. Glode anticipated involvement in a study of an unrelated vaccine (meningococcal conjugate vaccine) with Chiron Corporation. As Chair of the Pediatric Section of the National Medical Association (NMA), Dr. Sherrod received unrestricted educational grants from Merck, North American Vaccine and Connaught for a session on immunization at NMA's national convention in July. Dr. Thompson spoke at an NMA-sponsored scientific meeting which was partially funded by Connaught, but he received no honorarium. As Director for the Center for Vaccine Research at the University of California/Los Angeles, Dr. Ward reported some grants from Merck Sharpe & Dome and SKB, which constitute a small part of their total funding. Though he had no personal conflict,

Dr. Schoenbaum's wife owns stock in Amgen, Bristol Meyers Squibb, Glaxo and Proctor and Gamble.

Public Comment on Polio Vaccination Schedule

A public comment period followed for both individuals and organizations. Six minutes was allotted for each, with names drawn in random order. Clarifying questions only were permitted from the Committee. A brief financial disclosure was requested of the speakers, and most complied. In all, 21 statements were offered.

Speakers in favor of an IPV schedule were: Laurie S. Hunter of the Atlanta Post Polio Association, who contracted polio in 1979 after her son received oral poliovirus vaccine (OPV); Randy and Susan Pierson testified to their formerly healthy son Gordon's struggle with VAPP after receiving OPV at two months; Charles B. Moormon of Los Osos, CA, described his grandson Carl's vaccine-associated paralytic polio (VAPP), finally diagnosed by an elderly American and a foreign visiting physician; and Harvey Wilcox of Mobile, AL, discussed the challenges of his son's VAPP. Comments also were offered by Jerry Winkelstein, MD, of the Immune Deficiency Foundation; John Salamone of Oakton, VA and the HHS Vaccine Injury Compensation Board; and Michael S. Langan, MD, National Organization for Rare Disorders.

These speakers reminded the ACIP members of what VAPP can do to a child. They spoke eloquently of their own or their children's struggles, describing similar symptoms and disease development, and common diagnostic delays by clinicians who had never seen a case of polio. They lamented the pressure to maintain the status quo by physicians who think they know better, and asked how many children had been untreated and died undiagnosed by baffled doctors.

They described the parents' emotional and financial burdens, though significant, as inconsequential compared to their children's probable lifelong struggle to have a normal life. Repeatedly, they stressed that these tragedies need not have happened. They agreed that OPV's risk was not adequately conveyed, and also noted that though slim, the VAPP risk from inactivated poliovirus vaccine (IPV) also is worthy of consideration. While there was agreement that oral poliovirus vaccine (OPV) is appropriate in other areas of the world where polio is still endemic, this was not felt to be applicable in the U.S. All of them endorsed IPV, and some also supported a sequential schedule. Another speaker advocated no live polio administration. The significance of the vaccination schedule was also raised for consideration. Children with immune deficiency disease are vulnerable to live polio vaccine, but often are not diagnosed until their second year, and sometimes not until adolescence.

A change was urged in public policy to support the use of IPV until a child's immune system is developed, and to automatically test the child's immune system before administering OPV. The estimated 20 million Americans with rare disorders and primary immune deficiency diseases usually have been those affected in U.S. VAPP cases of the past 17 years. An all-IPV or mixed schedule was felt to be the best way to eliminate the only known cause of polio in the U.S.

It was noted that OPV's risk of VAPP also threatens public confidence in vaccines, which is essential to a national immunization program. (In fact, this public confidence was cited by both sides in the debate. IPV advocates cited negative reports on the pertussis vaccine several years earlier as a factor in lowered immunization and a rise in incidence. OPV advocates cited the risk of a change in shaking public confidence in both the vaccines and their schedule.) Several speakers discussed the slowness of actual awards from the Federal Vaccine Injury Compensation Program. The opinion was expressed that, even from a financial perspective, the increased IPV cost would be dwarfed by the annual cost of care for one child like Gordon Pierson ($350,000).

One speaker dismissed the theory that a U.S. change to IPV use would discourage or defeat the essential use of OPV overseas. Advocacy for "parental choice" was also perceived by one person as a screen for entrenched interests to battle a vaccine change. The Committee was urged to not abdicate its responsibility to make science-based public health recommendations to parents who may not be as well informed.

Speakers opposed to a change from OPV vaccine use were Philip Adler, MD, a Tampa, FL, pediatrician in practice for 40 years; Betsy Harris, RN, for Millicent Gorham, National Black Nurses' Association; Norma J. Goodwin, MD, Health Watch, Brooklyn NY; Ralph Buncher, MD, University of Cincinnati Medical Center/Institute for Science and Public Policy; Peter Paradiso, PhD, American Cyanamid Company, Lederle Praxis Biological Division; Evy Hay, RN, PhD, of MAP International; Richard Judelsohn, MD, Erie County Health Department, Buffalo, NY; George Carlo, MD, Chairman, Institute for Science and Public Policy; and Ana Rivas-Beck, JD, National Coalition of Hispanic Health and Human Services Organizations.

These speakers urged that several issues be addressed prior to any change in the ACIP recommendation. First, they cited a lack of data to prove that a sequential schedule would reduce the incidence of VAPP. Since *MMWR* had reported only eight confirmed annual case of VAPP in recent years, it was posited that false expectations of the proposed change's benefits may have been created. (However, Dr. Modlin noted that this may be more attributable to reporting delays than an actual drop in cases.) Research was urged, rather, on why the few annual cases of VAPP occurred, until the worldwide eradication program can eliminate both VAPP and wild polio. In the meantime, the potential importation of wild polio necessitates a solid immunity in the U.S. population. Polio's anticipated eradication by the year 2000 also presents a short window of benefit for a vaccination schedule change.

Concerns were voiced about reduced vaccination compliance, due to an increased number of injections or the alternative necessity of extra visits, raising the risk of other childhood diseases. The potential ethics of a change are particularly pertinent to poor families. Many of these may not speak English or know the U.S. vaccination regulations, and they may come from countries with still-endemic polio. Others are challenged by such practical problems as transportation for increased visits, the higher cost of IPV, or the inability of babysitters to have children immunized in clinics for their single mothers. These populations already have limited access to and utilization of services. For example, there is a 20%-lower immunization compliance by inner-city, particularly

African-American, children. And, only 42.9% of California's Hispanic children complete their immunizations by age two. They are more than seven times more likely to contract measles.

Before making any change in the recommendation, the CDC was strongly urged to conduct an in-depth public policy study, rigorously analyzing its potential national and international impact on overall immunization. The current schedule must be based on the reality of current options, not a hypothetical future. The anticipated amelioration by combination vaccines of increased injections and visits cannot be a factor until they are actually in use. Another concern expressed was the unknown impact of multiple vaccinations on vaccine effectiveness.

Aside from the increased time demands on practitioners in the managed care arena, the financial burdens of a schedule change were also cited as impediments. Analysis is needed to define who would pay the anticipated higher implementation and administrative costs, because alternatively, the required adjustments could reduce other public health practices and interventions. Done on a national basis, the change could unbalance the current system of health care delivery and outweigh any benefit.

The perspective of those working in the developing countries' polio eradication programs was presented. Although the pressure to eliminate OPV-induced VAPP is justified, those cases are overwhelmed by the unprotected thousands who need OPV. ACIP was advised to concentrate on global polio eradication and retain the OPV schedule. A change may affect the programs in the third world, which copy Western protocol, and perhaps even in the second world, which is more likely to copy Western technology. Such ripple effects could be devastating to these areas' already Herculean tasks to eliminate polio.

It was noted that OPV-related immunization policy has been the world's most successful immunization policy, and that the suggested changes have been compromises based on theoretical models. The control of childhood diseases must be based on scientific decision making, not compromise. The small countries with similar (but not identical) schedules as those proposed give no more than two injections at a time. This is facilitated by combination vaccine products not available in the U.S., by increased visits, or by withholding a hepatitis B vaccination.

Importantly, at least three doses of polio vaccine generally are given in the first year of life. The proposed schedule provides for two doses of IPV by four months, with boosters delayed to 12-18 months and 4-5 years of age. It drops the six month vaccination administration schedule that was adopted by ACIP to take advantage of the better immunization compliance rates in the first year. A recent Lederle-sponsored survey of 15,000 pediatricians was cited, which anticipated delayed immunization rates from increased injections, risking increased pertussis. The likelihood of disrupted infant vaccine delivery raises the prospect of polio introduction to the U.S. Polio eradication was offered as the answer, which will eliminate both VAPP and wild polio.

Other issues cited were the poor probability of implementing a sequential IPV/OPV schedule due to poor immunization record-keeping and mobile families, and the potential liability issues of

immunization options offered in examination rooms already crowded by problems of physical and psychosocial medicine.

Speakers in support of a IPV/OPV sequential schedule, were Kenneth Evans, MD, American Academy of Family Practitioners; Linda F. Golodner of the National Consumers League; Mary Kopp, RN, American Nurses League; I. Celine Hanson, MD, Texas Children's Hospital; and Carlton Meschievitz, MD, Connaught Laboratories, Inc.

A schedule of all-OPV, all-IPV or a sequential schedule of IPV followed by OPV was endorsed, as both these vaccines are used globally with remarkable success. IPV followed by OPV use would be in the best interests of public health, preventing the U.S.'s annual cases of VAPP. With increased use, the cost of IPV should drop, and surveys reflect parental preference for IPV's safety and willingness for extra visits. However, aggressive consumer and provider education are essential to ensure compliance. CDC's attention was directed to those speaking other languages, or to undereducated parents of children in migratory labor and rural communities, who have low reading comprehension.

A more scientific assessment of both the consumer and provider communities is needed. Data from recent research on provider knowledge showed that 95% used OPV as recommended by ACIP, but also showed rapidly declining knowledge on the contraindications of polio vaccine for immunocompromised recipients, immunocompromised household contacts, and other categories (including under-/unimmunized adults). There was a dramatic drop in knowledge by all on the third category.

Another study of screening procedures showed 5% of vaccine choices to be inappropriate according to ACIP recommendations. A review of recommendations showed that none (even CDC's and AAP's) address the issue of un- or under-immunized adults. These studies revealed as clear a need for rigorous education to providers as to consumers, in order to allow informed choice.

Pasteur Mérieux-Connaught also endorsed the sequential schedule and provision of clear guidance on the choices to practitioners. They have an adequate supply of both IPV and OPV, and have a license application pending for an acellular DTP (Tripedia^{R}) for infant use. Its safety advantages over whole-cell DTP should outweigh the extra shot required. The acellular DTP/Hib combination (PRP-T reconstituted with Tripedia^{R}), for use as a fourth dose in the second year of life, should be FDA-approved before any polio policy change is implemented. This should allow greater flexibility for year-two vaccine administration. An FDA license decision is expected in early 1997, and a mixed or all-IPV schedule could be implemented now.

Dr. Davis thanked all the speakers, and the meeting was adjourned for lunch.

Measles, Mumps and Rubella Policy Statement Presentation

Upon reconvening, the draft combination measles, mumps and rubella (MMR) policy statement was summarized by Dr. John Modlin. The MMR working group addressing the related issues had come to nearly unanimous agreement on several of the associated issues. Changes in the current draft

statement include (1) emphasis on the use of combined MMR vaccine for most indications; (2) a change in the recommended age for routine vaccination of the first dose of MMR, from 15 months to 12-15 months, and to 4-6 years for the second dose (MMR2); (3) a recommendation that all states take immediate steps to implement a two-dose MMR requirement for school entry; (4) discussion of the role of serologic screening to determine immunity; (5) strengthening of the recommendations for MMR vaccination of health care workers; (6) changes in the recommended interval between receipt of immune globulin and measles vaccination; and (7) updated information on adverse events and contraindications. Committee comment was also solicited on whether routine vaccinations for women of childbearing age should include those women who grew up outside of the U.S. (the current language), focusing on the rubella vaccination. Many of the recent rubella cases occurred in Hispanic women and their infants.

Second MMR Dose. The proposed language includes a routine MMR2 to be administered before a child enters school (4-6 years). A pre-adolescent vaccination at 11-12 years acts as a catch-up for those who have not received the second dose. The rationale is that the second dose prevents school outbreaks (origin of about two-thirds of the infections between 1985-1990). This would facilitate a harmonized timing of a routine second dose and could overcome the currently state-to-state variability in school policies that frustrates enforcing vaccinations.

There seems to be no difference in response to MMR2; the data suggest >99% accumulated seropositivity after the second dose regardless of age at administration. There is a slight but statistically significant increase in adverse events when MMR2 is administered at 10-12 years of age as opposed to 4-6 years. There is some evidence of waning immunity after the first dose of MMR, but this plays a minor role in outbreaks and measles transmission.

Discussion. Dr. Halsey reported the Redbook Committee's review of this question. They reaffirmed the need to check for evidence of immunity at 11-12 years and to administer two doses of measles vaccine. They also supported a policy of immunizing all schoolchildren by 2001. Their formal recommendation is in development, and will be official after review by their Executive Board. He suggested the CDC's document be worded to ensure it is not perceived as a retreat from providing a second dose at age 11-12.

Rubella in Unimmunized Women. Dr. Glode asked if the duration of rubella immunity was an issue in unimmunized women. Dr. Modlin reported rubella to be slightly more immunogenic than measles. The MMR working group considered a single vaccine dose to be sufficient evidence of immunity based on sufficient evidence. Secondary vaccine failures have not been a major problem, even given as young as 12 months of age. Dr. Sam Katz reported a rubella outbreak in North Carolina adults, with no spillover into the community. Those affected showed only an IgG response, not IgM, indicating a waning immunity. He also recommended that ACIP consider the availability of a combination MMRV vaccine by the year 2001; a second dose should perhaps be given for varicella.

Discussion. Dr. Nalin of Merck reported a paper in press of a study (since duplicated) which confirms no detectable rubella antibody at age 11 in cohorts of children with two doses prior to

school entry followed by one at 11 years. Though they do show immune memory and boost, the literature suggest that women with low level antibody can have inapparent wild rubella viremia upon contact with a case. This may indicate that in comparing two doses at elementary and middle school entry, the latter could have the advantage of carrying detectable titers into childbearing age to prevent asymptomatic or mildly symptomatic rubella in the 20% of women with immune memory but no detectable titer.

Dr. Griffin noted a waning of antibody, not immunity, and no U.S. evidence of waning immunity or increased susceptibility in a large portion of the population. But Dr. Nalin noted the stable seroprevalence for measles and mumps; only rubella's titers are waning. He suspected that this was a new phenomenon, which may produce some breakthroughs as this generation enters childbearing age.

Harmonizing Schedules. The next issue discussed was harmonizing schedules so that all children receive a routine second dose of MMR. Dr. Thompson favored doing everything possible to ensure that by 2001 all children in grades K-12 will be immunized, but noted that some states that implemented the second dose at the junior high level may be three years behind the goal. However, since the language only encourages states to meet that goal, a delay should not be embarrassing for those other states. He moved that the draft's language be accepted.

Dr. Guerra suggested language moving up the second dose of MMR in the case of community outbreaks, and allowing that to suffice for the second dose. Dr. Peter agreed, and to do so advocated stressing the draft's page 22 paragraph about adult vaccination. *Dr. Davis moved adoption of the draft's text, strongly recommending that all states take immediate steps to require two doses of MMR by school entry or kindergarten (4-6 years), and strongly recommending that all states take immediate steps to ensure that by 2001 all children in K-12 have been vaccinated with two doses of MMR.* Dr. DeBuono seconded the motion, which was unanimously approved.

Health Care Workers. At issue was whether to recommend routine MMR vaccination of currently employed health care workers (HCWs) versus those beginning employment. In recent data, Dr. John Watson reported that between 1985-1991, 795 out of 3000 measles cases in medical settings occurred in HCWs. About half occurred in hospitalized patients. Thirty percent of the cases in HCWs occurred in persons born pre-1957; 50% were unvaccinated; and 26% were hospitalized for a mean of seven days. About half provided direct patient care. In a seroprevalence survey of HCWs, 10% overall were considered susceptible to measles. Of those HCWs, five percent were born before 1957, 16% were born from 1960-1969, and about 33% were born from 1970-1979.

A median age of 35 years characterizes one current outbreak of ten measles cases in Bucks County, PA. Seven cases are among HCWs, two of whom were born before 1957. In another outbreak in Clark County, WA, the index case among 33 confirmed cases occurred in a Japanese exchange student, and the first transmission was to a high school student. In four medical facilities, nine HCWs and five patients have been infected. One HCW had no patient contact; three were born before 1957. Three thought they had (undocumented) vaccinations, and two HCWs received MMR after probable exposure.

Rubella information on HCWs is not as complete. Between 1994-1996, three outbreaks were identified involving at least one HCW. In one in 1994, 60% of cases occurred in adults, one occurred in a nurse in a shelter and three were hospital admission clerks. In another (1995), 95% of cases occurred in adults, one of whom was a primary care physician; two HCWs developed rubella 4-5 months after the outbreak, but no link could be found. Rubella and measles continue to occur in susceptible HCWs, and direct patient contact is not necessary. There is often some delay in diagnosing a case.

Program staff agreed that these few cited cases contitute a triumph, considering that HCWs constitute 5% of the entire U.S. workforce, but the high standard to cause no harm to patients still demands attention to this issue. The text of the proposed recommendation distributed to the Committee required (or alternately, recommended strong consideration that) all persons who work in medical and nursing facilities have documentation of presumptive evidence of immunity to measles/rubella. Mumps is not included.

One issue was whether to limit the recommendation to those beginning employment. HCWs are at increased risk of measles, the disease is not limited to new employees, and outbreak related vaccination programs for HCWs are difficult, disruptive and often too late to prevent the disease's spread. In light of low measles incidence, widespread HCW vaccinations may be thought low priority. Limitation to "high risk" groups or locations may complicate implementation, and "low risk" staff may rotate to "high risk" services.

Discussion. Dr. Schoenbaum raised the ethical issues of immunizing existing employees versus an applicant who could choose to work elsewhere, and imposing a potentially unnecessary risk in light of a low probability of contracting the natural disease. But Dr. Thompson disagreed; the risk posed by non-immune adults to patients made him want to extend this to virtually to all communicable diseases. Dr. Fleming reported HICPAC's preference for simple recommendations on such matters. They strongly supported the extension of these recommendations' to include all HCWs, especially those born before 1957, and preferred not to target certain groups.

Dr. Gardner noted that the majority of recent transmissions were from children to other unimmunized persons, not involving HCWs. He also noted that since the draft provides no clinical criteria for rubella, it essentially requires an expensive serologic proof of immunization. Dr. Halsey called for a strong reaffirmation in the statement for the immunity of HCWs working with pregnant women.

There are little data on adverse reactions to MMR among older employees, though the rates of such to rubella vaccine can be high in rubella-susceptible women/adults. Dr. Ward anecdotally reported high reaction rates to rubella immunization after his own recent screening among new employees 40+ years old. Data on such distinctions as age and staff responsibilities (e.g., patient contact) also are needed to formulate a national policy. If 80% of HCWs are probably immune to rubella, he suggested that perhaps vaccination should be mandated only for the remaining 20%.

In that case, Dr. Zimmerman quickly calculated that 12,000 HCWs would have to be vaccinated to prevent one HCW case, a very small return. There are also implementation implications when extending this policy to small group practices. Dr. Glezen likened this discussion to that of TB control in 1970; though not cost-effective, serious intent to eradicate disease required enhanced rather than reduced efforts. Dr. Schoenbaum demurred that not just cost effectiveness, but risk benefit assessments are needed, citing a greater HCW transmission of staphylococcal infections to patients than rubella or measles.

Dr. Fleming cautioned ACIP to avoid a double standard, observing that the same criteria should apply that were just used to vote millions to ensure a second dose of MMR to all schoolchildren. Dr. Davis agreed, but distinguished between cost and vaccine safety. He wanted information on the latter before deciding. More data was to be provided to the Committee, including that on cost effectiveness, to allow a productive discussion.

Distinguishing Vaccination Need by Year of Birth, Pre-/Post-1957. Those born before 1957, when measles was common, are currently considered immune and exempted. The proposed language provides that those working in medical and nursing facilities and without presumptive evidence of measles or rubella immunity (including those born before 1957), should receive a dose of MMR vaccine. A second dose should also be given as soon as possible, but at least one month after the first dose, to those born during or after 1957 who received only a single dose of MMR or other measles-containing vaccine and who lack other presumptive evidence of measles immunity. Alternative text specifies this without regard to year of birth. History of rubella disease (even if physician-documented) is always considered unacceptable evidence of immunity.

At issue is that HCWs born pre-1957 can be at risk for measles. Of the 1985-1992 measles cases in HCWs, 27% occurred in persons born before 1957. Dr. Gardner observed that the algorithm regarding measles history is moot; MMR will be required without a serological or diagnostic proof of rubella. There are no data on how reliable memory of measles or rubella can be.

Discussion. Dr. Schaffner endorsed testing new employees born before 1957 for susceptibility to rubella, and offering, but not requiring, a dose of MMR. Many institutions now automatically provide MMR for those born since 1957. He cautioned against yet more documentation for occupational health services, noting constrained hospital resources even for efforts in TB control or varicella immunization. He warned that attention to rarely-occurring diseases could minimize the impact of ACIP recommendations. Dr. Plotkin saw this as a reflection of the epidemiologic attention needed for vaccination of adults in the vaccine era, as opposed to when there were natural infections. He supported vaccinating HCWs born after 1957 as a sensible approach combining both epidemiology and cost-effectiveness.

MMR Use in HIV-Infected Persons. Dr. Will Schluter stated that the rationale for immunizing persons with HIV infection is that measles may cause them severe illness, and a 50% mortality among HIV-infected persons has been reported. MMR's safety in HIV-infected persons was supported to date by no reported serious or unusual adverse effects in those without prior evidence of severe immunosuppression.

However, a distributed draft *MMWR* article discussed a case of a 20 year-old male with Hemophilia A and HIV infection who received a second MMR dose in September 1992. Though asymptomatic, his CD4 T-lymphocyte count had been "too few to enumerate" in 1992, and he had declined antiretroviral therapy and prophylactic treatment for PCP. His symptoms and treatment until his death in December 1993 were described to the Committee. Measles virus was identified only upon examination of cultures from an open lung biopsy. Ribavirin therapy was begun and the patient stabilized, but over time his pulmonary infiltrates increased. CMV encephalitis was cited as cause of death, with pulmonary measles and MAC as contributing causes. In 1995, polymerase chain reaction amplification of the virus RNA showed almost complete homology with the measles (Moraten) vaccine strain used in the United States. CDC is conducting genomic sequence tests.

It was also reported that the seroconversion rates among HIV-positive children may be higher with earlier immunization. Two studies were cited showing a higher seroconversion rate (69% in the 1996 Arpadi study, 88% in the 1994 Rudy study) among HIV+ children 6-12 months of age than among those ≥12 months (50% and 79%, respectively). Several studies also were cited which demonstrated that failure to seroconvert correlates with a lower CD4 count (Palumbo 1992, Brena 1993, Brunell 1995 and Arpadi 1996).

Discussion. Dr. Gardner asked if there were viral cultures in the cited case that would have indicated measles when the PCP was diagnosed. Dr. Schluter thought not, though three bronchoscopies were done. There was no suspicion of measles until after the open lung biopsy. Dr. Katz reported that Dr. Bellini's CDC study showed that even those immunized HIV-positive children with 80%-90% seroconversion lose antibodies over the next 3-4 years. Therefore, it is unknown if successful seroconversion would protect against natural infection 2-3 years later. This should be considered regarding HIV-positive children. Dr. Schluter also cited the Al-Attar 1995 study which showed a loss of antibodies 30 months after immunization. In an older group, 4 out of 13 HIV+ children with a mean age of 5.5 years lost the measles antibody 2-5½ years after entry into the study. There are similar results from other studies of adults immunized before becoming HIV-infected.

Dr. Nalin was struck that the case individual became ill about a year after vaccination. NIH plans a study on whether vaccination can lead to chronic carriers of the vaccine strain. He wondered how many HIV-positive children immunized with the vaccine may be carrying a potentially mutating virus. He thought there was insufficient data to support such vaccination, and noted the package insert's advice against immunizing significantly immunocompromised persons with live vaccines. He also reported that the revised ACTG protocol advises examination of peripheral blood mononuclear cells, as well as of the respiratory tract through swabs and aspirates.

Dr. Gall asked if there were any data on primary or secondary immune responses to challenges subsequent to loss of antibody in HIV+ children, but none was known. Dr. Snider noted a similar issue raised with BCG vaccination, where vaccinated individuals developed disseminated BCG infection when immunocompetence dropped. Dr. Jenkins noted that this case challenges assumptions about vaccination. For example, the vaccine virus is assumed not to be transmissible, but that is a possibility with measles pneumonitis. It is possible that this person could have acquired the infection from someone with a similar condition. Dr. Paul Rota reported that preliminary data

from Dr. Bellini's laboratory indicated this to be a vaccine virus. He also commented that among the wild measles viruses, there is one related to the vaccine-like viruses. He noted the importance of examining genetic markers to differentiate between the vaccine strains and the wild viruses.

Dr. Halsey reported an Academy conference call on this issue. Their conclusion was to advise continued MMR for a child's first dose at about one year of age, but to exercise caution in significantly immunocompromised children. The challenge is to define the latter, and those guidelines are not yet finalized. The guidelines may be more applicable to the second than the first dose, and the CD4 count may require monitoring before the first dose.

Dr. Scheifele reported that all Canadian provinces are acting to implement second dose policies, and have conducted massive catch-up campaigns with school children. These are delivered by public health rather than the usual care providers, so their advisory notes were broader than usual. Rather than using CD4 counts, they advised them to consider deferring vaccination in any child with HIV infection who is receiving anti-retroviral therapy. This will be considered more in-depth.

As the report is ready for publication in *MMWR*, Dr. Schluter requested discussion on its final language. He proposed the following:

> "Testing for HIV infection is not necessary before administering MMR. MMR is recommended for asymptomatic and should be considered for symptomatic HIV-infected persons without evidence of severe immunosuppression. MMR should be withheld [it may be prudent to withhold] from HIV-infected persons with evidence of severe immunosuppression. MMR should be administered to HIV-infected infants at 12 months of age. The second dose of MMR should be given [as early as 15-18 months of age] [as early as one month after the first dose]."

The issues involved include whether this one case requires a new recommendation for HIV-infected patients, and if so, at what age to administer the first dose. There are limited data on immunogenicity at earlier ages. Another question is whether to immunize all HIV-infected children versus none for those with "advanced immunodeficiency", and to define the latter.

Dr. Halsey approved of the *MMWR* article except for the last paragraph's term "severely immunocompromised", and that its opinion differed from the Academy's cautiousness about the second dose. The article implies approval of MMR for an asymptomatic HIV person, but that was so of the case individual. He also advised caution about immunizing children at older ages, although the first dose at 12 months was acceptable. Finally, he expressed concern that additional cases may not have been diagnosed, due to the rarity of open lung biopsy for pneumonitis, though it is a common HIV manifestation as the disease progresses.

Dr. Gardner raised another implication of the second dose, that of persons who were immunized in childhood but now could not attend school without proof of a second dose of MMR. Dr. Katz said that the ACTG is studying the protocol for early administration, with the first dose at six months and the second at 12 months. He disagreed, however, with Dr. Scheifele's statement that anti-retrovirals indicate immunosuppression and severity of disease. Since the U.S. approach favors treatment,

many children may be put on early anti-retroviral therapies to ensure better outcomes by lowering virus load.

Dr. Davis stressed the need to define "immunocompromised". He also thought this case to be an extreme outlier, although he was concerned about the lack of data on any other potential cases. Dr. Margolis proposed using the CDC definition of Class III disease evidence of severe suppression to define a severely immunocompromised state. This could also involve children with no clinical evidence of disease, as it uses both age and a CD4 count: <750 in children under 12 months of age; <500 CD4 cells in ages 1-5, and <200 in 6-12 years. Dr. Griffin recommended using CD4 count for adults as well for ease of implementation. Dr. Modlin agreed that these are currently widely used and probably will remain so for some time, but he also noted increasing use of viral load markers.

Dr. Snider suggested recommending MMR for HIV-infected persons without measles immunity who are not severely immunosuppressed. A footnote could provide the definition of severe suppression and specify that this is an interim recommendation. Dr. Peter liked this approach, being reluctant to change national policy based on a single case. However, Dr. Davis was uncomfortable with definitions, concerned that this may block the use of vaccine in many children who need it, and this case may be an extreme outlier. He wanted to be convinced that CD4 <200 is a good benchmark, but lamented that there were no data to support it.

Several observations were offered. Dr. Sherrod asked if the concern was at what point children would not seroconvert, or where they would not be able to mount an immune response if challenged. Dr. Snider also wondered if the vaccine could speed the progression of HIV. Dr. Halsey cited the poor response to measles vaccine in the presence of immune suppression, as well as the accelerated loss of antibody after vaccination. Since there is no evidence that measles vaccine is effective in this population, he advised erring on the side of caution. By moving to definitions of severe immunosuppression, which the Academy also adopted in their conference call, the Committee is already allowing more immunizations than it would otherwise do. He encouraged placing the definitions and cutpoints into the body of the *MMWR* article. Dr. Zimmerman suggested simply stating this as a caution, and using a benchmark.

Dr. Peter suggested reviewing this question in conjunction with the Redbook Committee, and issuing an interim statement to provide guidance. Dr. Richard Steketee of the Division of HIV/AIDS Prevention noted the small number (5%-10%) of children in the severe immunosuppression category relative to the number of Level III infected infants in the 12-15 months age category. More than 50% of those would not respond to measles immunization. Dr. Katz noted the importance of this observation. Regrettably, this group is more likely to die from other diseases before a measles challenge.

Dr. Davis summarized the Committee's concurrence to use CDC's definition of severe immunosuppression. However, this was an interim recommendation which ACIP is evaluating this recommendation. Dr. Modlin agreed to work out the wording and return it to the Committee.

Use of Hepatitis Vaccine in the Vaccines for Children Program

After a short break, Dr. Margolis proposed adding groups at risk of hepatitis A to ACIP's earlier recommendations on the vaccines used in the Vaccines for Children (VFC) Program. The VFC program targets persons 18 years of age and under. The proposed additional groups would include men having sex with men (MSM), drug users, persons with clotting factor disorders and persons with chronic liver disease. He presented estimates of the number of persons in these categories who may be in need of vaccination.

Discussion. Dr. Davis noted that the two largest groups (MSM and drug users) would have to self-identify to get the vaccine. Dr. Margolis agreed, citing a recent *MMWR* article on poor immunization rates of MSMs for hepatitis B, who should also be vaccinated against hepatitis A. However, many are self-identifying, and education is increasing the numbers to whom health departments administer both vaccines.

Dr. Halsey thought the wording too vague on the potentially large group of drug users. He suggested, for example, specifying which drugs have been associated with hepatitis A as an alternative to waiting for and responding to local outbreaks. Dr. Margolis thought that such expansion of settings could help state epidemiologists and local health officials stop outbreaks. However, since all children using drugs cannot be vaccinated, it probably will be connected to community-wide epidemics.

When Dr. Scheifele asked clarification on "chronic liver disease", Dr. Margolis said "having some evidence of disease." It is restricted neither to severe disease nor to someone identified only through serologic screening. Dr. Halsey advocated vaccinating immunocompromised children who are chronic carriers of hepatitis B for hepatitis A, to protect them from further insults.

Dr. Margolis noted that the current recommendations primarily address persons with active liver disease, which raises concern regarding of fulminating hepatitis in a person with chronic liver disease. To change that would require changing the ACIP recommendation. Dr. Peter also observed that the word "susceptible" implies serological testing. Dr. Margolis agreed, but added that this text would apply to only a few children, and should not encourage a large testing initiative.

Dr. Davis agreed that the hepatitis A vaccine's purity and that it was a killed vaccine supports its early administration. However, Dr. Margolis noted a programmatic problem in the absence of a hepatitis A vaccination initiative. Data show an adverse outcome with disease, not with chronic infection. Dr. Halsey recommended against using the term "infection", as not everyone infected has the disease.

Dr. Davis' motion was seconded that the Committee continue to focus on the issues as initially presented. *Four categories of individuals were proposed for coverage with the hepatitis A vaccine supplied to the Vaccine for Children Program: men having sex with men, drug users, persons with clotting factor disorders, and persons with chronic liver disease.* Members in favor were Thompson, Schoenbaum, Glode, Griffin, and Davis; none were opposed. Abstentions were Ward,

Modlin, Guerra, and Sherrod. DeBuono was absent. The motion carried. Dr. Davis noted that all votes previous to this were in the affirmative with ten members present.

Dr. Hadler explained that the *MMWR* backlog of the last 1½ years has been due to staff limitations and expanded output. An editor is being sought. The varicella statement is being printed this week and due out next month. The adolescent statement is being edited, and hepatitis A would be next. Dr. Margolis reported that the *MMWR* editors are working on the ACIP statement, with an expected three months to publication. It was generally agreed that the issues discussed on this day did not require pulling the statement from publication. The hepatitis B statement would probably be released in August, but Dr. Davis requested an earlier date if possible.

Draft Statement for Rabies Post-Exposure Treatment

Dr. Charles Rupprecht updated the Committee on the draft rabies statement for less than conventional exposures. In background, he reported that though bat rabies cases had stabilized in the last few years, it is enzootic in the lower 48 states. There is a great diversity in the antigenic and genetic variants of bat rabies. Only a fraction of a percent of free-ranging bats have rabies; most bats do not. The problem is the increasing contact of humans and bats, and how to address prophylaxis.

Human rabies cases have declined from 10-12 per year in the 1940s to one or two per year now, but most cases are due to unknown sources of exposure. Rabies is under-reported due to the difficulty of detecting and diagnosing it, and because many of the populations at risk are not surveyed (e.g., the homeless). At least five human rabies cases since 1993 were not detected until autopsy. There has not been a rabies post-exposure treatment failure since the late 1970s. The majority of cases occur because many patients do not recognize that they were exposed. From 1980 to the present, there were 15 bat-associated rabies cases, only one of which would have been treated under current ACIP recommendations. In five deaths, no bat exposure or contact was reported. The remainder of human rabies cases had a history of bat contact, but not of confirmed bites. None of those would have met current ACIP recommendations for post exposure prophylaxis (PEP).

The clear majority of bat bite related cases were due to a single, rather rare rabies variant associated with the silver haired bat. In spite of its solitary nature, the variant from this species has been encountered by humans by either unrecognized direct exposure, spillover of the variant to more common bat species, transmission to a terrestrial reservoir like wildlife, or some unusual vector. Most cases are probably explainable by an unrecognized traditional bite exposure.

This variant appears to be adapted to lower temperatures and able to replicate in non-neuronal tissue. This indicates a peripherally invasive variant which could produce rabies fatalities from a bite or even a minor scratch. Therefore, bat rabies could warrant special public health attention because bats are ubiquitous. Bat rabies is enzootic, and the bites are small and potentially not recognized. Renewed public education about minimizing human contact with bats is advisable. Also desireable are the following: mandatory companion animal vaccination pre-exposure human vaccination for personnel at risk, prompt and proper post-exposure evaluation of exposed individuals. The species identification of bats submitted to diagnostic labs and public health departments, more study of

human/bat interaction and development of guidelines to indicate when physical exclusion of bats from human dwellings (as opposed to bat population reduction) is recommended.

The recommendation language presented during the last meeting was when a bat is present and the possibility of a bite cannot be reasonably excluded, PEP should be considered unless diagnostic tests for that specimen prove negative. Such wording has been proposed since the early 1990s. The National Association of State Public Health Veterinarians (NASPHV) PEP statement was strengthened to encourage PEP: "when a bat is present and the possibility of a bite or scratch cannot be excluded, PEP must be given" unless diagnostic tests are negative.

The question is, how prevalent is contact? Three studies were cited in which bat bites constitute only a small proportion of events requiring human PEP. This suggests that the current recommendations will not lead to significant PEP increases.

Dr. Rupprecht then reviewed the cost effectiveness of PEP changes. An algorithm assumed that PEP costs $3000, and the value of a human life in the literature ranges from $300,000 to $790,000 to $2 million. The ratio of PEP costs to the costs of the averted outcome produced varying thresholds at which PEP becomes "cost beneficial": 1%, 0.4% or 0.2% of the treated population would have fatally succumbed to rabies. This supports the new recommendations, as few PEPs have to be true positives to justify the treatment.

Discussion. Dr. Fleming asked if PEP was indicated for any human contact with bats, including virus excretion from saliva or bat guano. Dr. Rupprecht reported the environmental instability of the virus in guano, which is why colonial bats are not a more significant threat. The very limited data suggesting possible air transmission in bat caves have been questioned. Bat bites are so small that "non-bite" cases were probably more a nonrecognition of the bite.

Dr. Fleming agreed that the effect on PEP depends on the occurrence of a case, and asked how much of a change this recommendation would cause. He thought the publicity effect was a lamentable indication of the public health system's failure to incorporate those recommendations. Instances of bat contact are far greater than bat bites, but the public does not know to report these. He was concerned about a possible escalation of PEP with the new recommendation, as the data are still insufficient to assess its effect among an aggressively educated public.

Dr. Suzanne Jenkins reported an informal survey of public health veterinarians, all of whom had already instituted this definition. All but three had released this information at least through the public health networks, and none had yet reported increased PEP. The public health officials reported greater comfort with the proposed definition than the less definite previous recommendation.

Dr. Snider noted that inclusion of the word "must" in the NASPHV statement is regulatory and unlikely to survive CDC review. Dr. Griffin approved of the NASPHV statement, but advocated wording to allow individual local level implementation. Dr. Fleming agreed, advising changing the draft's "may be prudent to consider" to "should be considered". Dr. Thompson stated that anyone

treating a person who had encountered a bat would consider PEP, and advocated its clear recommendation.

Dr. DeBuono agreed, and suggested adding wording to address a scratch from a bat. When she noted that PEP is safe, just expensive, Dr. Fleming added that not all states provide free vaccine for PEP. Dr. Thompson asked if ACIP had the authority to add rabies vaccine to the VFC Program. Dr. Snider confirmed that, but Dr. Rupprecht presumed a negative cost benefit because so few children are at risk. However, many third-party payers compensate for PEP, including Medicaid. Dr. Rupprecht was not aware of any cases which persons sought but did not receive medical attention, nor are there data on cases reported to public health departments where rabies occurred after PEP was not offered.

Dr. Halsey suggested an ACIP recommendation that CDC work with CSTE to get the surveillance data needed to make recommendations. Dr. Rupprecht noted that the majority of PEP is delivered subsequent to indirect potential exposure to raccoon rabies. There is no global data on any human mortality from this, nor any ACIP recommendation to support it.

Dr. Griffin noted that text like "cannot exclude the possibility" is an impossible criteria, as the possibility of rabies contact can never be completely excluded. But if changed to "reasonable possibility", then most would recommend PEP. Dr. Halsey appreciated that as likely to avoid overtreatment, and suggested a formal request for state cooperation in collecting relevant survey data. The following wording for the ACIP rabies PEP statement was generated overnight, presented and approved on the following day:

> "Bats are increasingly implicated as significant wildlife reservoirs for variants of rabies virus transmitted to humans. Recent epidemiologic data suggest that seemingly insignificant physical contact with bats may result in viral transmission, even without a clear history of animal bite. In all instances of bat-human contact where rabies transmission is under consideration, the bat in question should be collected if possible and submitted for rabies testing. Rabies post-exposure prophylaxis (PEP) is recommended for all persons with bite, scratch or mucous membrane exposure to a bat, unless the bat is available for testing and is negative for evidence of rabies. The inability of care providers to elicit information surrounding potential exposures may be influenced by the limited injury inflicted by a bat bite (in comparison to lesions inflicted by terrestrial carnivores) or by circumstances that hinder accurate recall of events. Therefore, PEP is also appropriate even in the absence of a demonstrable bite or scratch, in situations in which there is reasonable probability that such contact occurred (e.g., a sleeping individual awakes to find a bat in the room, an adult witnesses a bat in the room with a previously unattended child, mentally challenged person, intoxicated individual, etc.). This recommendation, used in conjunction with current ACIP guidelines, should maximize a provider's ability to respond to situations where accurate exposure histories may not be obtainable, while still minimizing inappropriate PEP."

Voting in favor of the statement were Thompson, Sherrod, Schoenbaum, Guerra, Griffin, Modlin, DeBuono, and Davis. Drs. Ward and Glode were absent.

VOTE

The Committee expressed a willingness to consider including the rabies prophylaxis in the VFC program, but a cost assessment is needed. The members agreed to think about this and discuss it further in the future. The proposal would be developed by the Program with Drs. Griffin, Guerra, and Fleming. Dr. Rupprecht advised forming a working group to meet during the next year to help develop the statement, rather than requiring the attention of the whole Committee.

Timing of DTP4 -- Programmatic Issues Regarding Computerized Immunization Records

Dr. Kris Bisgard reviewed the current ACIP recommendation to administer the fourth dose of DTP vaccine (DTP4) at a minimum age of 12 months, and at a minimum interval of six months between DTP3 and DTP4. The 1994 recommendation states that doses administered at less than the recommended intervals should not be considered part of the primary series. New computer software facilitates the review of the age at immunization and the intervals between doses. At issue now is the action required upon receipt of DTP4 prior to a six month interval from receipt of DPT3, or when the child is younger than 12 months. She reported data on such vaccinations which occurred in 9.6% of 33,979 children in Alabama; and in 5% of a random sample of children aged ≥12 months in South Carolina.

There is a lack of immunogenicity and clinical efficacy data on early receipt of DTP4, as well as safety data on additional DTP doses from revaccination (e.g., a fifth dose prior to two years of age). For inactivated vaccines, there are data indicating increased boosting correlated to increased intervals between doses.

Dr. Bisgard showed a chart of the incidence of fever, redness, swelling and pain within 48 hours of DTP administration, which increases with each subsequent dose of both whole-cell and acellular vaccine. Measurements of diphtheria geometric mean titers (GMT) after children receive the primary series of three doses of DPT at 2, 4 and 6 months of age, and then again prior to the boosting dose at age 18 months, show that diphtheria antibody levels as well as the percent of seropositive children decrease prior to the boosting dose. These findings are similar for tetanus titers, except that most children remain seropositive after one dose of DPT. For both diphtheria and tetanus, titers increase substantially after a 12-month interval between receipt of the primary series and fourth dose. A similar pattern is seen with pertussis agglutinins titers and pertussis toxin antibody levels. A high GMT is achieved after receipt of the fourth DPT dose at 18 or 20 months of age, and after receipt of the primary series of DPT at 2, 4 and 6 months of age. Hepatitis B titers were also well boosted after an 8-month or 11-month interval from the primary series to the boosting dose.

The conclusion was that repeated vaccinations with DTP (e.g. repeating a fourth dose) is associated with an increased risk of adverse events, and there was no clearly demonstrated need. A two-month time interval is insufficient to produce sustained antibody levels or boosting. The issue is whether to count the fourth dose of DPT if it is given at less than the 6 month interval from receipt of DTP3

or at less than 12 months of age, or to revaccinate these children. A question is whether children who were given DTP4 inappropriately would benefit from having DTP4 repeated, as clinical efficacy and immunogenicity data are lacking, and preliminary data indicate no excess of pertussis in these children. On the other hand, increased numbers of adverse events are associated with increased doses.

The proposed program actions were to count a DTP4 vaccination if the interval from DTP3 was ≥4 months, or if the child was ≥12 months of age. In addition, programs should review vaccination tracking and scheduling in clinics where children are inappropriately vaccinated, educate providers on current ACIP recommendations, and monitor compliance with them. The new policy would be disseminated through a letter to state Immunization Program Directors. Broader associated issues include the need to create a computer algorithm to assess compliance with the current schedule. Another is to define the minimum acceptable interval for each dose and each vaccine for programmatic purposes, in order to define the usual recommended intervals between doses. This can be discussed further by a working group and during the October ACIP meeting.

Discussion. When Dr. Schoenbaum asked what happens if a child's vaccination is not counted, Dr. Bisgard responded that they are revaccinated. He then reflected that the adverse events in 10% of children may be more attributable to improved tracking than to the vaccine itself, and suggested a focus instead on provider education and monitoring. Dr. Bisgard agreed that this needed to be done, and noted associated programmatic issues such as whether Alabama should recall 3000 children for revaccination.

Dr. Halsey reported similar problems in other states, and the Redbook recommendation of no additional dose. He supported the option of intervals ≥4 months and to children ≥12 months, and recommended strengthening that with serologic data of a sample population to demonstrate adequate immunity. For ACIP, he defined the primary issue as the minimum acceptable interval between doses.

Dr. Thompson noted the need to properly direct public health staff. Dr. Zimmerman also cited the need for rules to guide the programmers developing the immunization software. Dr. Thompson recommended an interval between doses 3 and 4 of six months, but not to reimmunize if the first DTP vaccination is done in error after a three month interval. Dr. Snider agreed; the point is to correct any program deficiencies, but not to revaccinate.

Dr. Zimmerman observed that a one-month interval between DPT3 and DPT4 could be too little; it depends on the age of the child as well as the interval. He also noted that the Swedish trials' demonstration of falloff after the third dose of whole-cell vaccine would support a four-month interval. He recommended forming a working group to make those decisions. Dr. Guerra agreed, raising the complexity of the confounding variables, as infants are often immunized at multiples sites. The working group also should develop recommendations to parents whose child has been over-immunized.

Dr. Schoenbaum commented on the difficulty of establishing minimum acceptable intervals with so many different vaccine schedules. He also felt that offering two intervals would chance a mixed message, which should be avoided in ACIP statements. Dr. Ward agreed on the need to avoid confusion, but disagreed about the multiple intervals, since they are already being handled. He suggested guidance on the minimum acceptable and the minimum recommended interval. Dr. Peter suggested a minimum interval of four months, but to suggest a usual interval of 6-12 months. The accelerated schedule requires a fourth dose, which could be given as early as four months after.

Dr. Thompson recommended guidance to correct the clinical immunization procedure at ≤6 month intervals, but at ≤4 months to also reimmunize the child. The Program could advise practitioners, perhaps with ACIP guidance, if a mistake is made. However, concern was expressed that physicians do not have the access to quick response that a state program might; any standards must be publicized.

Dr. Paradiso was concerned at the difference of a 4-month minimum interval recommendation between dose 3 and 4 from the initial database for whole-cell pertussis vaccines. That schedule is 2,4,6, 18 or perhaps 15 months to do simultaneous vaccinations. The interval was changed to a 4th dose at 12 months, but always maintained six-month intervals between doses 3 and 4. Dr. Hadler added that the package inserts specify a minimum interval of six months. He advised the working group's careful assessment of the admittedly scarce data on intervals to help in clarifying possible situations such as these.

Dr. Schoenbaum advocated recommending whatever interval is felt to be ideal; that is how HEDIS addresses such questions. With strict criteria, each measurement set will produce program improvement. He also encouraged attention to those children missing the fourth dose rather than pursuing a fifth dose.

The membership of the existing working groups was to be checked before establishing another group to address these questions. With that, the Committee adjourned for the day at 6:26 P.M., and reconvened on the following morning at 8:38 A.M.

JUNE 20, 1996

Discussion of Draft Poliomyelitis Recommendation and Schedule

Dr. Ward noted that the polio vaccination schedule has been discussed for the past 2½ years, and presented the last working group discussions. The last major statement was released in 1982, with another revision in 1987. Two issues were to be addressed: the status of the recommended vaccination options, and their schedule.

Dr. Rebecca Prevots reported that 36 letters were received on the draft ACIP polio recommendations, many similar to the previous day's commentary. Many (17 letters) were received from polio survivors who favored expanded or sole use of IPV. The all-IPV advocates thought any use of OPV unacceptable due to the risk of VAPP. International health organizations favored a continued OPV schedule.

The IPV/OPV advocates thought the risk of VAPP unacceptable in the absence of wild virus. The all-OPV advocates feared that a change to a preferred sequential schedule could jeopardize global polio eradication, and worried about decreased immunization compliance for all vaccines due to increased injections and visits. They also cited the cost of IPV-based schedules, and the lack of evidence that a sequential schedule would reduce VAPP.

Supporters of equivalent options argued that this addressed the assurance of parental choice, and they emphasized the collateral need for parent/provider education. Dr. Sherrod suggested adding the previous day's points about the feasibility of implementation in light of four injections at 2,4 months, catch-up for the child behind in immunizations, and that increasing visits may decrease compliance and therefore create more immunization-related problems.

There were 121 confirmed polio cases with onsets from 1980-1996, and CDC is now reviewing 13 suspected cases with onsets between 1982-1996. Although most cases were reported within six months of the paralysis onset, many were also reported years later. There also can be a lag up to two years between the disease onset and confirmation, and entry into CDC's data system. All racial and ethnic groups were represented in the VAPP cases. The three case classification categories included vaccine recipients, contact transmission, and immune-deficient persons (vaccine recipients and contacts). The last few years have shown a decrease in contact cases and stability in vaccine recipient cases.

Dr. Glezen noted that only "typical" VAPP cases were reported and asked what would be atypical. For example, he feared missing many immunodeficient cases, which often are atypical. Dr. Prevots outlined CDC's review process, which includes external experts' review. Their majority opinion of "criteria met" determines classification as a confirmed paralytic polio case. Dr. Orenstein added that residual paralysis at 60 days after onset is required (the case definition); resolved paralysis would not be counted nor would encephalitis or other symptoms without paralysis be counted; the key definition is paralysis.

Dr. Halsey asked about the cost burden of continued care to persons who had paralysis but improved enough within 60 days. However, there were no data on such cases to include them in the analysis, nor were there data on the risk decades later of post-polio syndrome from wild polio, VAPP or improved cases. Dr. Strebel reported that NCHS is following up the natural history of survivors and of the post-polio syndrome.

Dr. Modlin commented that the peak time for most post-paralytic polio occurs about 25 years later. Since the first cases of VAPP appeared about 35 years ago, this would only now be seen. Dr. Katz noted this country's passive reporting as opposed to other countries' active surveillance of acute flaccid paralysis. However, Dr. Glezen cited a comparable 1963 Nebraska study in which a survey of flaccid paralysis produced 13 cases: three were Guillain-Barré and ten were paralytic polio with residual paralysis. All ten occurred within 15 days of OPV Type 3 administration, a rate of one case per 100,000 doses of OPV.

Dr. Modlin agreed; the National Vaccine Compensation Program data's low number of unreported cases (20%-30%) seems to indicate a problem more in case recognition than non-reporting. Dr. Evans reported that CDC received data from 1980-1992 on 100 identified cases, and the Vaccine Compensation Program identified 18 more.

Dr. Satcher asked if the rates of VAPP had been calculated by race, thinking that they would be consistent with immunization rates. However, these data were not available. Dr. Ward suspected that under-reporting may be likely because of lack of access to medical care. Dr. Orenstein thought that since most children receive OPV by school entry, distribution should reflect the population rates. The problem would lie more in the unimmunized pre-school population. Dr. Prevots reported on a 15-year study of VAPP in 13 nations analyzed by WHO. This showed similar general estimates to what is seen in the U.S.: one case from the first dose per million children who receive the vaccine.

Dr. Prevots then presented parental surveys of polio vaccine preference in 1995 and 1996. Three studies addressed feasibility of implementation. Of all parents surveyed, 46%-63% did not know that two polio vaccines were available. When asked which was preferred, most parents preferred the sequential or all-IPV schedule. The IPV vaccine was preferred due to OPV's risk of VAPP, but there was minimum concern over injections. If IPV were available, most parents wanted more visits to decrease the number of injections per visit, however, four injections were acceptable to 43% of parents. Of providers surveyed, 63%-74% in the public sector thought the schedule with minimum visits feasible (four between 2-24 months), versus 50%-71% in the private sector.

A preliminary summary of focus groups held by CDC to examine implementation issues was also presented. A group of Mexican migrant workers in Texas had low education and socioeconomic levels, but 55% knew of polio or had seen a victim. Most favored the new sequential schedule and accepted four injections in light of the child's protection, but 72% preferred injections spaced over several visits. A New York focus group hosted 18 African-American women with low incomes and education. They knew little about polio, but after education they preferred the new schedule's safer injection than OPV. A few thought four injections acceptable, but many were concerned about the side effects of four simultaneous injections and favored multiple visits.

Dr. Sherrod noted the studies that demonstrated providers as barriers, by not recognizing contraindications or educating their patients on disease. Terming provider education as key, she asked for data on providers' knowledge. Dr. Ward recalled data cited on the previous day by a concurring speaker, and agreed that education will be a major component of the statement. He also noted that though ACIP had voted for three acceptable options, the public testimony reflected concern about the practicality of implementing a sequential schedule.

Page 20 of the current statement addresses the problems raised by the absence of a combination vaccine. The suggested options to resolve the implementation problems were: (1) to schedule hepatitis B at 0, 1, 6 months to avoid injections at 2,4 months; (2) to schedule additional visits, or (3) to use OPV for a routine series.

Dr. Thompson defined the issue of number of injections as not one of pity for the child, but for the parents. The child would be no more outraged by three or four injections than it was for the first one or two. Though he expected parents' objections, he also thought they would allow the four injections during a single visit. He urged that the standard be set for simultaneous administration of all vaccines. Dr. Halsey also noted that this transition period will hopefully only require four injections during a visit for a few months. And, if the new recommendation is implemented by CDC in early 1997, it could help the approval process for the combination vaccines.

Options for Reducing the Number of Injections

Dr. Prevots introduced discussion of how the schedule would be implemented. The committee had been surveyed on various options to reduce the number of injections, based on the following assumptions: (1) that DTaP is licensed for use in infants, (2) that the new combination vaccines are not yet available, and (3) that the hepatitis B vaccine is given at birth and IPV is recommended at 2,4 months.

When asked how best to implement the two IPV doses of the sequential schedule, six of the ten members favored three injections at two months, and most felt that implementing the preferred schedule was feasible. When asked what recommendation should be made to time the hepatitis B doses, most of the members chose 0,1, and 6 months. Dr. Hardegree noted that this matches the package insert.

"Preferred" Wording

Dr. Prevots summarized the use of the word "Preferred" in the new statement. On the first page, it states: "for overall public health benefit, ACIP prefers a sequential schedule..."; on page three, "a sequential IPV/OPV schedule would be preferred..." and on page 17, "use of IPV followed by OPV is the preferred option..."

Dr. Thompson observed that the ACIP had already voted unanimously to favor the sequential schedule although it accepted the other two. He advised replacing "ACIP prefers" on page one with "ACIP recommends", since ACIP is responsible to recommend on public health activity. After that, the parent can choose. He was agreeable to the rest of the text. Dr. DeBuono agreed, but also counseled consistency throughout the recommendations, and more assertive language. She also advocated stating the benefit of IPV alone under some circumstances. Dr. Ward reported ASTHO's preference for the stronger language of "recommended".

Dr. Sherrod objected, however, that the public health benefit had not been as sufficiently analyzed as the scientific benefit. She criticized the missing analysis of potential risks in implementation, and called for a risk-benefit analysis of decreased compliance, lower immunization, and possible resurgence of disease. She advocated delaying any recommendation until that was done. Earlier in the meeting, Dr. Carlo had offered to supply the formal protocols for such a formal policy analysis.

Dr. DeBuono raised the Committee's commitment to the sequential schedule, evidenced by its previous vote not to exclusively recommend IPV, but to move toward it. However, Dr. Zimmerman

felt that moving from the word "preferred" would contradict that previous vote, raise legal issues, thwart informed decision and choice, and put physicians in the difficult position of presenting an option and then a recommendation. Since expert opinion is divided as to what is the best policy, he urged the Committee to stick with its original language for a sequential schedule.

Dr. Sherrod asked what was voted in October. Dr. Hadler summarized the three-page guidelines for an ACIP statement, to the effect that ACIP recommended expanded use of IPV. An IPV regimen was preferred when the risk of reintroduction of wild polio virus was remote and there were no overriding concerns about an all-IPV schedule. Until an all-IPV schedule could be universally recommended, the preferred U.S. recommended schedule was a sequence of IPV/OPV vaccinations. This transition schedule would most likely be two doses of IPV at 2,4 months, followed by two doses of OPV, with the timing to be determined.

This sequential schedule was expected to reduce the frequency of VAPP by 50%-75% or more, and facilitate the transfer to an all-IPV schedule. Physicians would be urged to expand the use of IPV. The IPV/OPV schedule would not require additional injections in the second year of life. The recommendation had been adopted unanimously by the members voting on this issue. This summary was confirmed from the meeting minutes.

Dr. Thompson moved to substitute the word "recommends" for "prefers" on page one, and was seconded by Dr. DeBuono. Voting In favor were Thompson, Schoenbaum, Guerra, Griffin, DeBuono, and Davis. Voting against were Ward and Glode (by telephone link). Sherrod and Modlin abstained.

VOTE

To general agreement, Dr. Thompson thought "preferred" on page three's second paragraph to be appropriate usage ("... ACIP considered a range...and concluded the IPV/OPV strategy would be preferred for overall public health benefit"). However, on page 17 *Dr. DeBuono moved that both the "preferreds" be changed to "recommended".* The motion was seconded. She later amended her motion to state *"Although schedules using only IPV or OPV are both effective and are acceptable options for preventing poliomyelitis, the ACIP recommends the use of IPV followed by OPV for primary poliovirus vaccination of children in the U.S., because, (1)..."* The motion was seconded. In favor were Thompson, Schoenbaum, Guerra, Griffin, DeBuono, Davis, and Ward; Glode voted against (by telephone link), and Modlin and Sherrod abstained.

VOTE

Dr. Satcher suggested to general agreement that citations of research needs be included in all ACIP recommendations. To allow a vote on Dr. Zimmerman's suggestion, *Dr. Ward moved to insert "fully" to read "fully acceptable"* on pages 1 and 17, regarding the administration of OPV or IPV alone. Dr. Glode seconded the motion. However, Thompson, Schoenbaum, Guerra, Griffin, DeBuono, and Davis were opposed. Ward, Modlin, and Sherrod abstained; none were in favor. Dr. Glode then hung up her telephone link, having left written comments with Dr. Davis.

Vaccine Schedule Options

In background to the vaccine schedule options, Dr. Prevots reported the ACIP agreement in February 1996 that all polio vaccination schedules should be consistent regarding age of dose administration. In May, the working group reviewed the proposed schedule of options used for administration of IPV alone, OPV alone, or the sequential use of IPV/OPV.

The factors involved include (1) consistency with current vaccine package inserts for OPV and IPV; (2) the potential impact on parental/provider compliance and resultant coverage; (3) the timing for achieving mucosal immunity with a sequential IPV/OPV schedule; and (4) the impact on reduction of VAPP among immunologically abnormal recipients of OPV with a sequential schedule. The assumptions are that (1) the first two doses of polio vaccine for all schedules would be given at 2,4 months; (2) administering doses in the second year could result in lower coverage (this was supported by data from the National Immunization Survey); (3) two doses of OPV are needed for adequate mucosal immunity and (4) later administration of the first dose of OPV resulted in greater time to diagnose immunodeficiency, with consequent decrease in VAPP in immunodeficient children.

Dr. Prevots presented the five discussed schedules. Schedule 1 immunize at 2,4,6, 18 months, and 4-6 years; Schedule 2 at 2,4, and 12-18 months and 4-6 years; Schedule 3 at 2,4, 6-12 and 12-18 months; Schedule 4 at 2,4, 6-12 months and 12 months-6 years; and Schedule 5 at 2,4, 6-15 months, and 15 months-6 years.

Dr. Ward then summarized the working group's discussion. All the schedules provide adequate individual immunity, but only Schedule 2 is currently consistent with package labeling and compatible with a harmonized polio schedule. This confirmed the February ACIP vote. Schedule 2 provides the greatest advantage in decreasing VAPP since the first OPV dose is delayed to 12 months. However, it may decrease coverage, as the third dose is given after the first year of life. Schedule 3 provides the greatest advantage regarding mucosal immunity, since all four doses are given by age 18 months.

The difference in immunization rates is probably slight between 2, 4, and 6-18 months versus the 2, 4, and 12-18 month schedule for polio vaccination, though the existing data are not precise. There was agreement on the need for a school entry booster dose, a problem with Schedule 3, which completes immunizations at 18 months and provides no booster. The differences in reduction of VAPP by age of the first OPV dose relates to the age at which their immunodeficiency is first recognized. These cases constitute about one-third of recipient cases; the data suggest an even older age at which many immune deficiencies are recognized, which supports delaying OPV to the second year. This is another argument for Schedule 2.

Discussion. There were two formal votes during this meeting on the schedule, with the second being a contingency vote should the FDA allow the package insert change. Dr. DeBuono clarified to Dr. Ward's agreement that in a survey of ACIP members, eight supported the first doses at 2,4 months. The current issue is when the third dose would be given. The polio vaccine doses now given at 2,4,6 months would change to 2,4, and 12-18 months, and the third dose could be OPV. Dr. Davis added

that an all-IPV schedule would not give any injection at six months; the earliest third dose would be at 12 months.

Dr. Halsey noted that the asterisk on the draft's table was inconsistent with the package insert, which specifies OPV/IPV at four and 12 months. The asterisk was to be deleted. Dr. Ward summarized that the current insert schedule is 2, 4, 12-18 months, and 4-6 years for OPV; however, though inconsistent with the package insert, most OPV vaccine is given at six months. He observed that this is also the current IPV schedule. With an FDA change allowing IPV at six months, these protocols would be completely compatible. The working group noted two problems with a sequential schedule in which OPV is given at 6 months: it is inconsistent with the package insert and it presents risks to immunodeficient vaccine recipients. They voted to recommend the second schedule (the current IPV schedule) with a footnote that if OPV only is administered, it can be given as early as six months. Dr. Peter advocated for the footnote, if only to avoid the appearance that ACIP is rescinding its recommendation of two years previous.

Dr. Thompson moved that the Committee adopt the working group's schedule (IPV 2,4 months, and OPV 12-18 months and 4-6 years). Voting in favor were Thompson, Schoenbaum, Guerra, Griffin, DeBuono, Ward, and Davis. None were opposed. Sherrod and Modlin abstained, and Glode was absent.

VOTE

Alternate Vaccine Schedule

Next, the Committee addressed its approach should the FDA approve a schedule change. Schedule 1 was the current OPV schedule (2, 4, 6-18 months, 4-6 years). It was noted that this is standard practice, though slightly different from the package insert. Dr. Ward summarized that there is an application to FDA to change the package insert such that the IPV and OPV schedules would be matched, extending the allowable time for the third dose to six months. Then, all OPV and all IPV could be unified under Schedule 1, a more flexible schedule with wider age windows for immunization. Schedule 2 is the current IPV schedule, and conforms to the current package insert; this was the option just adopted as the sequential schedule.

Dr. Satcher made the point that there are no data to inform the impact of OPV at 6-12 months versus 12-18 months in the sequential schedule. Dr. Hadler specified that while there are data on immunogenicity, there was none to indicate the effect on immunocompromised persons, the most likely point of impact.

Vote. Dr. Davis called for a straw vote on the favored schedule if FDA changes the package insert. With FDA approval, five members favored retaining Schedule 2 and three members favored Option 1 for administration of all IPV, all OPV or an IPV/OPV schedule.

Further Discussion on Draft Recommendations

Dr. DeBuono suggested eliminating the clause on page 24 indicating that an all-IPV schedule is preferred "if the vaccination status of household members is unknown". This virtually ensures all-IPV administration to the child, as the immunization status of everyone in the household often may

not be known. Dr. Thompson agreed; if unsure, the physician should just proceed with a sequential schedule. If certain of an unimmunized household member, the IPV schedule should be used.

Dr. Griffin raised a related issue on page 15, where the text seems to suggest an unfeasible practice of vaccinating parents or care givers simultaneous with the infant. Dr. Guerra also disliked imposing an additional implementation layer on the front line caregivers, and advised further deliberation. Dr. Schoenbaum thought the risk of shedding virus in high titers to be small in an IPV-inoculated child at the time of the first OPV dose. He also suspected that most family members with unknown vaccination records were probably fully- or partially vaccinated. Dr. Ward thought there was sufficient committee agreement to remove the page 24 text, but the more serious issue on page 15 presented implications requiring more thought by CDC staff.

As a result of this day's decisions, Dr. Fleming worried about children in clinics who do not fit with the sequential schedule. For example, he wondered if a child with two doses of OPV followed by two of IPV would be considered completely immunized; or if the doses were mixed, if the provider could supplement them. Dr. Ward responded that the harmonized schedule simplifies that, since all schedules provide for four doses. Dr. Orenstein agreed, recalling the 1982 statement which also accepted four doses of any type. Dr. Halsey added that this would be consistent with the Redbook Committee vote to accept four doses of any kind by school entry.

Discussion of Needed Research

The next issue discussed was future research needs, as raised by Dr. Sherrod. Data in the post-recommendation phase should be monitored to assess the statement's implementation. Dr. Davis advocated use of the sensitive National Immunization Survey, which can monitor progress and implementation on a quarterly basis to within two percentage points.

Dr. Sherrod recommended an active surveillance system for ongoing tracking of immunizations timing, similar to a registry. Dr. Orenstein noted that other assessments are also being conducted. Dr. Peter urged establishing a baseline as soon as possible, if the schedule change was not only to reduce or eliminate VAPP but also to elevate the surveillance of flaccid paralysis. Dr. Ward noted that increased surveillance may also reveal more VAPP. This provides yet another strong argument for an all-IPV schedule, Dr. Peter observed.

The Committee then offered its recommendations for research. Dr. Davis wished to maximize registries to ensure good coverage. Dr. Thompson emphasized research toward the rapid development of combination vaccines. Dr. Schoenbaum wanted not just to examine VAPP, but to determine whether anything occurs due to increased use of IPV. Dr. Guerra wished to develop a methodology to assess evolving knowledge by recipients, parents, and providers, perhaps focusing on providers. Dr. Ward stressed a focus on education to ensure that parents and providers can make a knowledgeable choice. Dr. Davis agreed, noting that this could extend beyond polio vaccination to refine other immunization programs.

Dr. Sherrod called for education on and the monitoring of a possible resurgence of vaccine-preventable diseases. Dr. Davis reported that NIP is working hard with the states to monitor

immunization levels. Dr. Guerra wanted to monitor the supply and inventory of IPV and OPV doses to assess any change in usage trends. Dr. DeBuono called for movement beyond passive and active surveillance systems, to CDC-funded urban and rural sites to assess issues of compliance with visits and other immunizations. She thought this particularly important in light of opposition from Hispanic and other groups based on compliance and additional injections. Dr. Hadler reported that such pilot activity is planned; if successful, it can be adapted elsewhere.

Dr. Ward proposed that CDC staff list potential activities to develop these suggestions at the October meeting. Dr. Snider also suggested that Committee members re-review the statement for other potential research areas. Dr. Peter added, regarding implementation coordination between the public and private sectors, to develop targets of coordination with professional organizations (e.g., publishing an *MMWR* with the issuance of a recommendation). Dr. Snider recalled previous attempts to do that which could be updated, along with generating a comprehensive list of actions needed before implementation could take place.

Statement on Prevention of Pneumococcal Disease

With that, the Committee took a short break, after which Dr. Schoenbaum summarized the nearly-final pneumococcal statement. It references all the known literature, provides a table of published studies of pneumococcal vaccine efficacy and recommendations for vaccine use keyed to the strength of the evidence. It also provides one part of an algorithm for vaccinating populations aged ≥65 years. One question is whether the algorithm should address the overall recommendation, or just concentrate on this one segment of the population.

The statement is still incomplete in addressing cost effectiveness. Dr. Schoenbaum reported that Dr. Sisk's progressing work on this had produced increasingly encouraging data. As of the previous week, the vaccine could be cost-saving for adults with pneumococcal bacteremia. He asked for a July 12th turnaround for Committee comments, reminding the members that 10,000 adults would die this year of pneumococcal bacteremia.

Pertussis Vaccine Statement Update

Dr. Peter Strebel recalled an October 1995 presentation to ACIP from manufacturers on six of seven vaccine efficacy studies and their interpretation. These were detailed in Rome in November 1995 and updated at the NIH meeting in Washington D.C. At the February 1996 ACIP meeting, a presentation from Wyeth-Lederle described results of their vaccine study. CDC staff then listed the criteria supporting use of DTaP vaccine, and discussed key policy questions involved in recommendations for vaccine use.

The NIH meeting reports showed acellular products to be associated with a lower frequency of local and moderate reactions compared with whole-cell pertussis vaccines; seven of eight acellular vaccines had an efficacy in the range of 70-85%. It was agreed, however, that much still is to be learned about the pathogenesis of pertussis, and the mechanisms of immune response. As of this ACIP meeting, there were licensure applications at FDA for more than three acellular products.

Therefore, the time had arrived for a draft statement on acellular vaccines. The Committee's written comments were solicited on the draft as outlined by Dr. Dalya Guris. The draft statement provides an overview of whole-cell (DTP) and acellular (DTaP) pertussis vaccines. A preference for acellular vaccines is stated. The draft discusses the vaccines' use, side effects and adverse reactions, and precautions and contraindications. At this time Tripedia^{R} was specificaly included because it is the only acellular pertussis vaccine reviewed by FDA and likely to be the first vaccine licensed for use in infants.

Dr. Guris summarized that ACEL-IMUNE and Tripedia^{R} have been licensed for doses four and five. Recent trials have demonstrated a high efficacy of DTaP vaccines comparable to DTP, with fewer local/systemic and certain serious adverse events. There are currently four DTPs licensed in the U.S., with 70-90% effectiveness. This draft also addresses adverse events following DTP.

Pertussis trends were described. Reported incidence has increased in the U.S. since the 1980s, with a distinct resurgence in 1993. The DTP efficacy estimates from recent European trials wre in the range of 36%-93%. The draft statement provides general information on the acellular pertussis vaccine: its contents, the mid-1980s Swedish trial, and licensure of ACEL-IMUNE and Tripedia^{R}. Table #2 in the statement outlines the efficacy studies of eight DTaPs used as initial doses in infants.

The statement's introduction addresses the immunogenicity, clinical efficacy and safety of the vaccine. In the multicenter acellular pertussis trial (MAPT), no DTaP yielded the lowest or highest immune response to all of its antigens. However, there also was no correlation shown between antibody response and clinical protection against pertussis.

Direct study comparisons were precluded due to differences in design, case definition, and schedule. Randomized double-blind controlled trials and observational designs estimated absolute vaccine efficacy. These were summarized in Table 2. Table 3 outlined vaccine safety and summarized mild and local systemic reactions. Overall, acellular vaccine had 30%-99% fewer adverse events compared to whole-cell vaccines. Table 4 outlined the moderate to severe reactions. No data were available on the rare severe reactions, but this was to be monitored through post-marketing surveillance.

Dr. Schaffner was surprised at the statement's lengthy discussion of the trials. As they have been reported extensively in the literature, he suggested summarizing this information for the end user. Dr. Guris responded that this could be done.

Dr. Guris then discussed Tripedia^{R}, the information on which begins on the draft's page nine. Table 5 presents its immunogenicity data for the first three doses. A booster given at age 15-20 months showed a four-fold antibody rise in more than 92% of infants. She reported the clinical efficacy results for the Swedish trial in which two doses at 5-11 months showed vaccine efficacy of 47%-82% for cough of any duration, and 57%-90% for cough of)30 days. The German study (three doses at 2,4,6 months) showed a 94% efficacy (65%-99%) for DTaP, and 97% (73%-99%) for DTP for paroxysmal cough of ≥21 days.

The statement continues with data on Tripedia[R]'s safety. The U.S. study showed 50%-85% fewer mild reactions than to DTP; the German study showed moderate to severe reactions (per 1000 doses, 0.11 for unusual crying of ≥3 hours, 0.03 for febrile seizures, 0.05 for hypertonic hyper-responsive episode [HHE]). For severe reactions, the German study showed rates similar to DTP recipients for invasive bacterial infections, deaths, and hospitalizations. But none of the invasive bacterial infections or deaths were thought to be causally related to DTaP. The Vaccine Adverse Event Reporting System (VAERS) data of five million DTaP doses administered during 1991-1993 showed significantly lower rates of adverse effects than for DTP, and reported no encephalopathy. When simultaneously administered, 93%-100% of children evidenced seroconversion to Hib, polio serotypes 1-3, and HepB. However, these results involved small numbers of children.

Subsequently, Dr. Strebel presented the results of the February ACIP working group discussions, as voted upon by seven Committee members and two liaisons. Acellular vaccine was preferred by seven members for the first three doses, highly preferred by one, and may be preferred by one. Whole-cell vaccine was felt a permissible alternative by three, not felt so by three, and three required more information before deciding. Seven felt there was a need for a fourth dose of acellular vaccine, and two did not. Four wanted this to be administered at 12-18 months, three at 15-18 months, and two needed more data. Eight felt there was a need for a fifth dose of vaccine at 4-6 years. And, seven felt that acellular pertussis vaccine "should be preferred" for the fourth and fifth doses.

Dr. Plotkin thought whole-cell vaccines to be an acceptable alternative. ACIP had defended them in the past as effective with some safety problems, but justified by the protection afforded; reversing that would seem self-contradictory. Second, most of the studies summarized showed whole-cell vaccine more effective than acellular. This carries more weight in developing countries than in the U.S., but must be considered. He wished to avoid any effective "interdiction" in the U.S., due only to safety issues and disregarding effectiveness. Finally, he thought the evidence was still insufficient on whether the booster schedules for acellular vaccine would be different than those for current whole-cell vaccines'.

But Dr. Ward disagreed. He noted that ACIP continually re-evaluates the risks and benefits of the issues brought before it, with pertussis as with polio. He termed the acellular vaccine safer and possibly more efficacious than some whole-cell products. However, based on the evidence and with better products, he suggested that perhaps ACIP should state a "recommendation" rather than a "preference" for acellular vaccine.

Dr. Strebel reviewed the other questions posed to the working group. On the interchangeability of different acellular and whole-cell vaccines, seven thought DTaP could be used to complete a primary series begun with a whole-cell vaccine, and two were uncertain. Six thought it acceptable to use a second acellular vaccine for the fourth and fifth doses if an acellular vaccine was used previously, but three were unsure. The opinion was split on whether different acellular vaccines could be used interchangeably for a primary series, with three in favor, three opposed, and two uncertain.

Regarding precautions, Dr. Strebel presented the scenario of a reaction considered as a precaution for subsequent DTP: e.g., ≥40°C fever, persistent inconsolable crying, HHE, or a convulsion. If this

followed a dose of whole-cell vaccine, could acellular vaccine be administered for subsequent doses? In a vote, all seven wanted more data.

The issues for this meeting included (1) an *ACIP preference for DTaP* for all doses. A straw vote was unanimous to recommend use of DTaP for all five doses. Other issues were (2) the recommended age for the fourth dose, (3) whether whole-cell DTP would be an acceptable alternative, and (4) interchangeability.

Regarding *whether whole-cell DTP would be an acceptable alternative*, a footnote currently indicates its acceptability as an alternative to DTaP for any of the five doses. If agreed, this would allow a smoother transition, and still allow DTP-Hib combinations. Cost factors will favor use of the whole-cell vaccine. A no vote by ACIP would stop whole-cell use faster, but be more expensive as existing stocks would be discarded.

Regarding the latter, Dr. Griffin wished for some alternative like DTP being considered acceptable during the transition period from whole-cell to acellular vaccine. Dr. Ward agreed, but still advocated language to encourage distancing from whole-cell vaccine, such as "not preferred but acceptable". Dr. Thompson drew parallels to non-discouragement of the older typhoid vaccine when a cleaner one was released, and the same just done for polio vaccines. He favored acknowledging that whole-cell is an acceptable alternative while clearly recommending the acellular pertussis vaccine.

Dr. Strebel then asked about the *recommended age for the fourth dose of DTaP* (Tripedia^{R}). First, a 12-18 month schedule allows a dose at 12 months. The earlier age allows higher coverage but less antibody boosting, and a possible short interval problem between doses three and four. This also conflicts with the acellular package label. Second, a 15-month schedule (or 6-12 months after the third dose) is the current recommendation. The 15-18 month schedule is supported by data. The later age provides the best boosting, but possibly lower coverage.

Dr. Hadler asked the manufacturers to comment on their data relating to indications for the fourth dose; however, little data exist. Dr. Jill Hackell of Wyeth Lederle Vaccines and Pediatrics reported no data yet from their studies of children 12-15 months of age, but that the efficacy study seems to support a fourth dose at age 15 months. Dr. Corry Dekker of Chiron Corporation reported testing the fourth dose starting at 15 months, but they are still investigating the need for a fourth dose and are assessing the Italian study. In the data to date, three doses look good.

Due to the paucity of data, Dr. Ward suggested using the whole-cell schedule as a benchmark until data to indicate fewer doses or a more restricted age emerged. Dr. DeBuono agreed. Dr. Hadler thought the package label was not explicit except for the six month interval. Dr. Hardegree agreed, but reminded the panel that the package labels can be changed based on what the data support.

Dr. Strebel then asked about the *interchangeability of acellular vaccines for the fourth and fifth doses*. If Tripedia^{R} is licensed for infants, there will be one acellular pertussis vaccine (Tripedia^{R})

for all five doses of the schedule, and one acellular vaccine (ACEL-IMUNE) licensed for only the fourth or fifth dose.

He presented three different situations for children, and the implications of his question. Interchangeability could be found unacceptable because (1) there are no data on efficacy, (2) there are different antigen preparations that may affect antigen response from a different primary series, (3) doses must be repeated if the product is unknown, and (4) there could be possible overvaccination. Acceptability could be indicated if either PT or FHA were present in the vaccine used for the primary series, and in the vaccine used to boost. Some immunogenicity data indicate that all acellulars boost well after a whole-cell primary series. This would lead to acceptance of prior doses.

Dr. Modlin asked about the risk of under-immunization, since many children must receive doses four and five at different sites than the primary series. Dr. Orenstein acknowledged that risk, but the only alternative would be for clinics to stock all vaccines or send the children home for a later return. Since that is not feasible, a prohibition of mixing and matching would be unacceptable.

Dr. Halsey advocated dropping the word "recommend", advising instead text like that used for Hib vaccines: "when feasible, the same vaccine should be used". Dr. Snider agreed, to avoid any interpretation prohibiting a switch if vaccination with whole-cell was already done. Dr. Strebel suggested the text "the primary vaccine series should be completed with the same acellular pertussis vaccine, if it is known and available..." Dr. Ward found that wording acceptable.

Dr. Peter commented that the issue pertains more to the first three than the last two doses. The labelling will have to be carefully viewed. Dr. Snider asked if there were any objections to using the Hib wording for all doses. Dr. Sherrod had none, but noted again that there were no data to support the interchangeability in the primary series. Dr. Hardegree emphasized that the NIH is collecting immunogenicity and safety data, not data on efficacy for prevention of clinical disease. Dr. Schoenbaum noted that this presented another reason to ensure that the recommendations indicate their sources. He and Dr. Sherrod urged clarity that though no data are available, the recommendation was based on the best current knowledge.

Dr. Strebel then reviewed the recommendation for *simultaneous administration of vaccines with acellular pertussis* vaccines during the first and subsequent years. In the first year of life, DTaP + Hib, OPV (or IPV), and hepatitis B were recommended; in the second to sixth years, DTaP + Hib, OPV (or IPV), MMR, varicella, and hepatitis B. The contraindications were an immediate anaphylactic reaction (resulting in no further vaccination, with D,T or aP/wP); and acute encephalopathy within seven days (in which case DT should be used for subsequent doses). Precautions were indicated for a temperature of ≥40.5°C (105°F) within 48 hours, collapse or shock-like state (HHE) within 48 hours, persistent inconsolable crying lasting ≥3 hours within 48 hours (though this should perhaps be reconsidered), and convulsions with or without fever within three days.

Dr. Snider asked about the data on the frequency of contraindications following DTaP. Dr. Strebel responded that some are becoming available from the acellular vaccine trial, but the results were not yet known. The children with the rare reactions need to be studied and followed up with acellular vaccine. Also to be considered are a personal history of seizures, in which an unstable neurological condition would postpone vaccination. A stable neurologic condition would indicate DTaP with acetaminophen. A family history of seizures would also indicate this. No further pertussis vaccination would be required after a case of culture-proven pertussis. Vaccination of persons ≥7 years of age was not routinely recommended, except perhaps experimentally for outbreak control (e.g., in hospitals or school settings).

Dr. Strebel welcomed written feedback by July 19 on either the full draft or the response sheet provided to the Committee. Dr. Peter urged careful consideration of the precautions and contraindications, which were derived from experience with whole-cell rather than acellular vaccine. He recommended a fresh look, and no assumption that the precautions and contraindications are the same. Dr. Orenstein thought that the vaccines should be considered individually. While he was concerned that any adverse reaction could be labeled vaccine-related without supporting data, he also noted an as-high incidence of 105° fever for DTP as DTaP. Dr. Snider noted the potential helpfulness of manufacturers' data to ACIP.

Dr. Jill Hackell noted that the timing of the statement would define which products might be included. Dr. Davis agreed; CDC would attempt to include those products which were licensed by the *MMWR* publication deadline. Dr. Hadler suggested that a short statement could be issued on the vaccines licensed after the statement publication.

Dr. Scheifele cited the lack of data on the safety of the fifth dose of acellular pertussis vaccine delivered in a continuous series. He anecdotally reported his own recent study of local reactions to the fifth dose, showing no difference between acellular and whole-cell pertussis vaccines. This may have been foreshadowed by the increase of reactogenicity in the 18-month dose. He suggested that a light formulation or adjusted timing of the fifth dose may be advised, and he advised caution in the wording used.

Vote on DTaP for the Vaccines for Children Program

Dr. Hadler led a discussion on whether DTaP should be recommended for use in the Vaccines for Children (VFC) program for infants. This was a unique proposal for ACIP, which had never before voted to provide VFC with an as-yet unlicensed product. But if DTaP is licensed this summer, this would avoid a recommendation gap until the next ACIP meeting. He noted the ACIP preference for this vaccine to whole-cell vaccine, and that the data presented showed acellular vaccine as effective as whole-cell for preventing pertussis. A recommendation would allow the government to establish a federal contract for VFC's vaccine use before the October 1996 ACIP meeting. He suggested a vote with certain stipulations. The recommendation wording had been submitted to the Committee.

In discussion, Dr. Ward advocated allowing a 12-18 month dose, and Dr. Hadler suggested eliminating the specification that this recommendation is only for infants. Dr. Hardegree agreed, raising the issue of primary immunization for children older than one year of age. Dr. Halsey also

noted that the current VFC approval is for 12-18 months administration, but that they use these at nine months for a child who is behind schedule. Dr. Orenstein agreed to delete the recommendation's second bullet detailing the immunization schedule. The Program would develop the timing of vaccinations for the statement. The final approved wording read:

> "The ACIP approves the use of DTaP vaccine for all five of the DTP series for prevention of diphtheria, tetanus and pertussis in the Vaccines for Children Program, subject to each of the following conditions: (1) the DTaP vaccine is approved for this use by the Food and Drug Administration; (2) the ACIP has published a notice in the *Morbidity and Mortality Weekly Report* recommending the use of DTaP vaccines for all five doses; and (3) a Federal contract for purchase of DTaP vaccine for use in all five doses has been established. The ACIP recommends approval of the DTaP vaccine for the Vaccines for Children Program."

A favorable vote on this acellular pertussis vaccine language was cast by Davis, Thompson, Sherrod, Schoenbaum, Griffin, and DeBuono. None were opposed. Abstaining were Ward, Guerra, and Modlin; and Glode was absent. The vote carried.

VOTE

Recommendation Process Discussion

After a lunch break, Dr. Snider conveyed Dr. Satcher's sincere appreciation to all for their work and valuable comments on the polio recommendation. He expressed comfort with the Committee's decisions and asked for suggestions about unmet research needs. He advocated that the statement identify the areas in which the Committee attempted to make a decision but for which more information is needed. Dr. Snider noted the uniqueness of this statement's development process. While valuable, this will not necessarily be routine; future statements' process will be decided on a case-by-case basis. The Committee's input to the recommendations development process was welcomed.

Dr. Sherrod asked the purpose of public input, as no issues were reconsidered by the Committee. However, Dr. Ward disagreed: his own views on the immunization schedule were affected by public input, as were the added research issues to the agenda. Dr. Snider noted the value of the previous day's input to those ACIP members who had not attended the IOM meeting. He also observed the clear recognition that there are two phases to this process: the Committee's recommendation, and CDC's consideration and perhaps acceptance of it.

Dr. Schoenbaum recalled a routine Director's presence at this Committee 25-30 years earlier. He agreed with both Dr. Sherrod and Ward that though the Committee had not formally discussed the public input, it was individually significant to the members. He also noted that the more structured the policy analysis is, the clearer and more explicit the research needs will be, and they are better identified during the process than at the end. Dr. Snider noted that Dr. Sherrod wished to be added to the process and procedures working group.

It was agreed that substantive comments on the polio statement would be reviewed by Dr. Ward, Dr. Davis and the Program staff. Dr. Hadler suggested that the working group draft a plan to monitor the recommendation and further address the research agenda. It would then go to the Director in the next month or two, and be released in January or February. A research section could be added. Dr. Davis requested each member's input on the current draft be sent to him or Dr. Ward.

Dr. Sherrod asked about the timetable for the important component of provider and public education. Dr. Orenstein summarized the CDC recommendation process, which includes developing education materials, evaluating physician knowledge, etc. The polio recommendation would be no exception. Dr. Hadler recalled that a survey of the public health sector last summer indicated a possible recommendation implementation in 3-6 months. Dr. Thompson urged all to keep in mind, while working to enhance the statement, that each month would add another case of VAPP that could be avoided with an issued recommendation.

Vaccination of Premature Infants

Dr. Genevieve Losonsky, of the Center for Vaccine Development and Associate Professor of Pediatric Medicine at the University of Maryland, reviewed the current status of vaccination of premature infants. Premature infants are among the specialized groups warranting further attention and study to see how they respond to immunizations compared to full-term infants. Premature infants are an important population; 7% of 4.3 million live births are premature infants, and about 300,000 survive annually. The mortality of those born weighing 1500 grams or more declined from 50% in the 1950s to 2-3% in the 1990s; for those ≤1000 g, from 90% in 1960 to 30% now.

Considerations pertinent to a premature baby's response to immunization include developmental immunologic maturity and antigenic exposure immunization maturity. Studies of the serologic response of premature infants to HBV after three doses showed less than optimal seroconversion rates, providing the impetus for an ACIP change to delay immunizations to a weight of 2000g or two months of age. A U.S. study has addressed questions of ethnic differences in immunization, immunogenicity of vaccines used overseas, and infants born of carrier mothers in the U.S. who need to be immunized at birth. The cohort of 118 children was divided into three birth weight groups: <1000g, 1000-1500g, and >1500g. The exclusion criteria omitted infants of carrier mothers, those who may be immunodeficient and those who received antibody, or any other variable than prematurity that might affect immunogenicity.

The Merck HBV vaccine was given to infants in their first week, the second dose at two months, and the third at 6-7 months. Infants in the <1000g, and 1000-1500g groups had less than optimal responses after three doses of Hep B vaccine; 50%-60% did not achieve protective levels of antibody. But the >1500g group were very comparable to data on full term infants. Ninety percent of the non-responder infants were in the <1500g birth weight group, and the magnitude of response also diminished in this group. Dr. Losonsky clarified that GMT groups were done only on responders.

She then summarized the limited literature on vaccines given outside the neonatal period. DPT was given to 110 infants at Johns Hopkins in the 1980s, with gestational age (GA) of 33-37 weeks, mean

birth weight of 1700g and scheduled immunizations at 2,4, and 6 months. The responses were equivalent to full-term infants. The same was true of another study evaluating 16 children 23-28 weeks GA of lower birth weights (835g), which only looked at antibody response after the third dose of tetanus for responses. Again, OPV administered at 2,4, and 6 months to 20 infants of 29-37 weeks GA, produced an equivalent response to full-term babies.

Two other studies were summarized of IPV and OPV administered to small groups (<20 children). The first, in Buffalo in the early 1990s, gave IPV (enhanced) at 2,4, and 12 months to 25-35 week GA children (no birth weight was reported). This produced a 42% response rate to PV1 and PV2 after the first dose, but the same systemic and mucosal immune responses as in full-term infants after the second dose. The second study examined IPV, eIPV and OPV, given at 2,4 months to sixteen children with a mean weight of 800g. A 60% decreased response rate (31% protective level) to poliovirus Type 3 was shown after two doses. In the same group, the response to hemophilus influenza Type B (Hib) was studied. After the third dose, they were equivalent (100% protected) to full term children. In another study, PRP-OMP vaccine administered at 2,4 months to infants 26-34 weeks GA produced a decreased response rate and lower magnitude of response compared to full term infants.

Dr. Losonsky then outlined vaccine reactogenicity in premature infants. Her own study showed minimal, all local reactions in <1% of all infants. Dr. Orenstein asked if there were control infants, and she said no, since that the selection was based on GA, not birth weight. However, they did look at full-term historical controls. Dr. Orenstein noted that an 8% result is only 1/13 the children, and was not sure the data implied a causal relationship between vaccine and adverse events.

Dr. Losonsky continued that early studies contain no reports of reactogenicity with polio vaccines. There have been extensive studies of larger premature infants with DTP, again with no adverse reactions. But the Pichichero study found 85 severe reactions, and three children with increased oxygen requirements after getting DPT. Dr. Evans elaborated on two case reports: one child who had a third DTP before discharge, who died; and another off the ventilator who received DTP, decompensated, and died within two weeks. There was pre-existing lung disease, but also clearly a clinical change after the vaccination.

She stated that the final consideration for premature infants is not presence of active immunity, but passive immunity, and what deficiencies might emerge. She shared a chart showing that the majority of antibody transfer occurs in the last two months of gestation. A pilot study is now being done with NIP and Dr. Bellini at CDC to assess the susceptibility to measles of low birth weight premature infants. Forty percent of children <1000g had antibodies, which dropped to zero at 2-4 months. None, including those >1500g, had antibodies after six months.

Three conclusions were offered: (1) the vaccine schedules effective in full-term infants are not always applicable unchanged to premature infants (certainly true of HBV and perhaps other vaccines); (2) poor responses to vaccination in premature infants, when seen, seem to be dependent on GA and weight at the first vaccination; and (3) it is difficult to predict which vaccines or antigenic types will result in poor immunogenicity.

Discussion. Dr. Peter asked for the Academy and Redbook perspective from their current recommendations, noting the small subject numbers in the data cited. Dr. Losonsky agreed; more research is needed on how well the premature infant responds. She thought the current Redbook recommendation on Hep B appropriate, though perhaps a bit more conservative then necessary. Its cutoff is 2000g, and the data suggest 90% of non-responders are in the <1500g birth weight group. There may be more room to vaccinate children of lower birth weights. This is a pertinent consideration in terms of compliance and trying to reach a captive population. Perhaps final study analyses may indicate how to tailor vaccinations.

Dr. Halsey asked if GA might be a better measure than birth weight, but Dr. Losonsky preferred birth weight, as assignment of GA to premature infants can be off by two weeks either way, or a potential four-week total overlap. Dr. Halsey noted that other guidelines recommend waiting until two months of chronological age, and asked if she agreed. This may be particularly acceptable with hepatitis B, but since the risk to an infant with an antigen-negative mother is low, it may be better to wait longer to generate a better response. Dr. Losonsky knew of recommendations to delay hepatitis B to two months, but was aware of no studies about vaccine response after two months.

Dr. Glezen knew of some studies on pathogenicity and safety, referenced in Vaccine Compensation Program claims. Cases cited reactions to DTP in two month old premature infants. One large study of children discharged by two months saw no excess events, but another study of babies still in the nursery (a smaller group) found adverse effects related to DTP. These have not yet been published or peer-reviewed. He asked if babies not old enough for discharge should be immunized. Dr. Losonsky responded that they do not do so for children on ventilators. She anticipated emerging data on the response of children to acellular pertussis vaccines.

Dr. Sherrod noted that apnea, oxygen responses and other outcomes could be due to other stimuli, and suggested to Dr. Losonsky's agreement that these should be examined in a more controlled environment. Dr. Chen reported a retrospective Kaiser study on Dr. Sherrod's point that should provide future data.

Dr. Davis noted the interesting competing issues between the need to delay HBV, while a rapid loss of measles antibody indicates a need for earlier immunization. Perhaps MMR might be used to provide protection, though disregarded for immunization purposes. These children need more doses in a tighter time frame, and the risk factors causing prematurity in the first place also must be considered regarding such variables as likelihood of return visits. Dr. Losonsky agreed.

Dr. Peter advocated the Committee's proactivity in supporting the need for more research. He also suggested that infants born to carrier mothers who are immunized with hepatitis B vaccine at birth to carrier mothers who have a poor response probably should receive a fourth dose. He thought this preferable to serological screening. While the Redbook has a chapter on premature infants, the COID also are frustrated by the lack of data. Dr. Losonsky reported that she had data on the lack of response to a fourth dose, a complex issue, but had had no time to present it. Dr. Snider suggested bringing this issue up at the interagency group so as to stimulate a response.

Update on the Vaccine Injury Compensation Program

Dr. Jeff Evans reported that of 5,042 claims filed, 3,533 had been adjudicated and $663.1 million awarded. He then updated the Committee on changes to the Vaccine Injury Table, Section 312 of the National Childhood Vaccine Injury Act. These changes related to pertussis and rubella vaccines, and were inserted after IOM reviews. The 1991 IOM report removed residual seizure disorder and HHE under DTP vaccine, added chronic arthritis under rubella-containing vaccines, and clarified the definition of encephalopathy.

The 1993 IOM report added brachial neuritis and removed encephalopathy under tetanus-containing vaccines, added thrombocytopenia under measles-containing vaccines, and removed residual seizure disorder under MMR vaccines. It also added hepatitis B, Hib and varicella vaccines to the VIT, and added a general category for any new vaccine recommended by CDC for "routine administration to children".

There were three challenges to the ruling, which were denied by the Circuit Court of Appeals in March 1996. The court affirmed the HHS Secretary's authority to amend the Qualifications and Aids to Interpretation accompanying the Table, ruled that the Secretary consulted sufficiently with the Advisory Commission on Childhood Vaccines on the changes and the final rule; and sustained the HHS position that absence of definitive evidence for a causal relation permits a condition's removal from the Table.

With the court's decision, work is beginning on over 108 pending claims, with the first few determining if there is evidence in the literature that DTP causes permanent neurologic damage. He would report further on this to the Program. They are currently finishing the process of adding the 1993 IOM report's conditions to the rule. He also reported that Congress had not yet acted on the "vaccine tax" ("51 cents for preventive disease").

Dr. Evans stated that the parents' concerns expressed at this meeting must be considered. However, he also reminded everyone that the compensation process is litigious. While HHS can recommend on who is eligible for compensation, the courts make the decision, and the parties work out the final compensation amounts. The involvement of severe disabilities also usually engages other issues and slows the process.

However, the average time to final compensation is 2.8 years, still less than the tort system's average of seven years. He reported that 87 of about 220 OPV injury cases (half from the 1960s/1970s, half from 1980s/1990s) have been compensated at $40 million. The cases for vaccines administered after October 1, 1988 will cover past and future unreimbursed expenses, after insurance reimbursements. However, as mentioned by Mr. Wilcox, Medicaid claims upon the compensation award may further delay direct payment to the families. He clarified that the 1995 increase in claims related to the deadline for claim submission prior to March 10th to qualify under the old tables.

National Vaccine Program Office Report

Dr. Robert Breiman of the National Vaccine Program Office (NVPO) then reported to the Committee. He is the Acting Director; the position announcement for Director nominations will

close on June 28. The NVPO coordinates the federal vaccine activities of groups such as CDC, HRSA, DOD, USAID, FDA, NIH, and NVAC. It has four goals, which are described in the published National Vaccine Plan: (1) to develop new and improved vaccines; (2) to ensure the optimal safety and effectiveness of vaccines/immunizations; (3) to better educate the public and health professionals on the benefits and risks of immunizations; and (4) to achieve a better use of existing vaccines to prevent disease, disability and death.

The NVPO was transferred in June 1995 to CDC from the office of the Assistant Secretary of Health. However, it arrived with little funding, and CDC supports it from year to year. They have an unmet needs research budget of about $6 million, for which this year they considered 105 proposals from various agencies. The bulk went to research on vaccine safety (c. $3 million), about $1.5 million to research and development, about $15,000 funded to education, and about $1 million to coverage.

The ACIP and the NVPO advisory Committee (NVAC) are symbiotic. The latter attends to policy, while ACIP attends to the technical aspects of immunization. He then outlined their ongoing activities: (1) addressing new approaches for surveillance and funding for vaccine safety; (2) investigating the use of non-traditional providers for adult immunization (pharmacists, nurses, etc.); (3) providing guidelines for partnerships (e.g., improving a relationship with academia, industry and public health to maximize research); (4) working to overcome obstacles to vaccine research and development; (5) establishing immunization information systems (NVAC will issue a paper on confidentiality issues); and (6) assisting in preparation of the Pandemic Influenza Preparedness Plan. When ready, NVAC will provide opinion on the plan and coordinate its promotion with the organizations that wrote it.

Dr. Snider solicited member nominations for NVPO Director. He reported that the NVPO is also part of his responsibilities, and welcomed the NVP/NVAC/ACIP's synergistic opportunity to avoid program overlap. He noted that the NIP supports both NVPO and NVAC. NVAC meets in Washington D.C. with representatives from the Secretary's office and members of other agencies. To facilitate interactions as much as possible between the ACIP and the NVPO, Dr. Schoenbaum volunteered to attend the Pandemic Influenza Preparedness Plan meetings.

Unfinished Business

Dr. Davis requested responses to the polio plan by July 12 and to the pertussis statement by July 19. Comments on the *MMWR* articles were hoped for within a week, and on the recommendations by July 8th, but he acknowledged that this schedule may have to be delayed. He then asked for further public comment. With no response, he thanked everyone for their participation and the meeting adjourned at 3:25 P.M.

I hereby certify that, to the best of my knowledge, the foregoing minutes are accurate and complete.

Jeffrey P. Davis, M.D.
Chairman, Advisory Committee on
Immunization Practices

5/5/97
Date

MEMORANDUM FOR THE RECORD

This memorandum is an addendum to the June 1996 minutes of the Advisory Committee on Immuniztion Practices. This memorefects correction received after the minutes were finalized.

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